TUMORS OF BONE

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TO OUR WIVES

M C G *and* J B C

IN APPRECIATION OF THEIR LOYAL

ASSISTANCE AND UNDERSTANDING

Preface to the Third Edition

The twelve years that have elapsed since the second edition have witnessed the introduction of a number of new entities in neoplasms of bone and in skeletal diseases of unknown etiology The increase in the scope of this book has led to the inclusion of a number of new chapters such as those devoted to fibrous dysplasia, osteoid osteoma, tumors of the spine endocrine changes in bone and rare diseases of bone. The chapters on embryology of bone and chondroblastomas have been entirely rewritten as well as the chapter on treatment of sarcoma of bone. The tabulations of bone tumors, which represent the fundamental material on which this book is based, have been extended to include more than 500 additional cases. More than 100 new illustrations have been added and a large number of old ones replaced. The object has been to present the best possible reproductions of representative roentgenograms, gross specimens and photomicrographs.

Twenty years have now elapsed since the authors began their review of the material on record in the Surgical Pathological Laboratory and a correlation of the pathologic and clinical findings with follow-up results. Through the courtesy of Dr Arnold Rice Rich, Professor of Pathology at Johns Hopkins Hospital, it has been possible to consult the original records in conjunction with recent follow-up reports. These follow-up results have served to justify our original classifications in regard to such disputed entities as benign giant-cell tumor benign and malignant chondroblastoma, chondrosarcoma and Ewing's endothelial myeloma. The authors are deeply indebted to the Commonwealth Fund, the Office of Research and Invention of the United States Navy and the National Cancer Institute of the United States Public Health Service for their financial assistance in maintaining continuity of the clinical and pathologic records and the results of treatment over a period of time that extends back to 1893. They gratefully acknowledge the contribution from the Geschickter Fund for Medical Research, which has aided in the publication of this book. They also wish to thank the publishers for their cooperation in the tedious task of resetting the entire work.

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Acknowledgments

The authors owe a debt of gratitude to innumerable colleagues and associates who have contributed clinical data, sections, roentgenograms and specimens to build up an ever increasing library of source materials over the past twenty years. This revision would not be possible without their aid and that of the loyal technical staffs at Georgetown University Medical Center and the U. S. Naval Medical Center, Bethesda, Maryland. The authors wish to thank Dr. W. W. Ayres and N. M. Starky for their collaboration in photomicrography, Dr. M. J. O'Leary Matthews for reading the proof and Leoda Danner, Marjorie Johnston, N. Elaine Wilcox and Dorothy Lord for aiding in the follow-up studies.

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Preface to the First Edition

Developments in roentgenology the use of radium as a therapeutic agent and more thorough histologic studies have reawakened interest in the subject of bone tumors. This renewed interest and the large amount of material accumulated in the Surgical Pathological Laboratory in the Johns Hopkins Hospital have led to the preparation and publication of this book. It is hoped that the studies recorded here will result in a more simple classification of these tumors, increased accuracy in diagnosis and better methods of treatment.

This material was made available through the labors of Dr Joseph Colt Bloodgood, Clinical Professor of Surgery in the Johns Hopkins Medical School, and to him and to Dr Dean Lewis, Professor of Surgery grateful acknowledgment is made for the opportunities afforded in the pursuit of this work.

The authors also desire to make the following acknowledgments to

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INTERPRETATION OF CLINICAL FINDINGS

DEAN LEWIS M D

The formulation of a more uniform classification of tumors of bone based upon a better understanding and correlation of the clinical, roentgenologic and pathologic pictures has aided materially in the diagnosis and treatment of these lesions. The diagnosis of malignant lesions of bone is being made at an earlier stage and with greater certainty than ever before. In young patients the accurate diagnosis of such lesions as Christian's disease, Ewing's sarcoma, leukemia in bone and osteogenic sarcoma is being made with ever increasing frequency The improvement in diagnosis is due to careful studies by the clinician and the resort to biopsy In the adult, several diseases such as Paget's osteitis deformans, von Recklinghausen's polycystic disease, multiple myeloma and metastatic carcinoma with generalized skeletal involvement are found. Chemical studies may give valuable diagnostic aid, for in osteitis deformans the blood phosphatase is high blood calcium is high in von Recklinghausen's disease serum proteins are high in multiple myeloma. We should no longer be content to determine whether the bone lesion is benign or malignant. The kind of bone disease and the variety of sarcoma must be determined, for the treatment to be instituted and the prognosis vary with the histologic picture.

Recently the roentgen findings have been emphasized—in some cases to the neglect of the gross clinical picture. In the diagnosis of a malignant tumor all diagnostic aids should be employed. Some of the outstanding clinical features will be reviewed and discussed.

PAIN

Not infrequently the earliest clinical sign of a developing sarcoma is pain or a feeling of discomfort. The pain associated with a malignant growth of bone is extremely variable and presents nothing characteristic. It may be absent or so slight that it neither arouses the suspicion of the physician nor demands the attention of the patient. At times it is described as drawing in character It may be noted only when the extremity is used. Frequently it is described as rheumatic in character As the intensity varies, so does the mode of onset. In some cases pain develops gradually while in others it comes on suddenly even without an exciting cause, such as trauma. In cases with an acute onset, with fever resembling closely that of acute osteomyelitis, pain may be throbbing or boring in character not unlike that associated with inflammatory disease of bone. Pain may even be intermittent, disappearing from time to time, to reappear Such remissions of pain, especially if the objective findings are not marked, may veil somewhat the clinical picture and lead to false conclusions concerning the diagnosis. Such a remission may lead to some doubt regarding the nature of a lesion which is progressive. Intermittent pain is also noted in syphilis of bone and sclerosing nonsuppurative osteomyelitis. Tenderness, like spontaneous pain, varies considerably Pain noted when the extremity is moved may be absent upon pressure or when the tumor is tapped.

A patient with a central giant-cell tumor usually complains of some pain, which is frequently described as rheumatic. This

pain differs in no way from that associated with a bone cyst. When a pathologic fracture occurs through the expanded cortex about a central giant-cell tumor the degree of pain already experienced is not necessarily increased. I have seen a patient with a central giant-cell tumor of the lower end of the femur who suffered no increase of pain when the fracture occurred. The fracture was suspected when the column of support was lost. Intense pain is usually experienced when a fracture is caused by a metastatic carcinoma of bone.

Inspection and Palpation

The soft parts covering a malignant tumor of bone are usually easily displaceable over it unless the tumor has involved these parts, has undergone degeneration with cyst formation, the soft parts becoming adherent, or an inflammatory lesion has been superimposed upon the pre-existing lesion. The veins of the skin are usually enlarged and prominent. Distinct venous markings in the skin over the tumor are frequently one of the most striking manifestations. The skin usually has a peculiar color—a cyanotic redness—which the experienced clinician recognizes as one of the striking clinical features of sarcoma. This same peculiar discoloration is found, for example, in sarcoma of the breast and sarcoma of the soft parts In those cases in which the underlying tumor has softened and undergone cyst formation the skin may be adherent and reddened. Adherent, reddened skin, associated with fluctuation following softening, may simulate closely an inflammatory lesion. Ulceration of the skin occurs much more frequently with carcinoma than with sarcoma.

The size of a sarcoma of bone varies within wide limits. Variation in size naturally depends upon the location of the tumor the histology of the growth, the length of time it has existed, its relation to the surrounding structures and whether they offer resistance enough to the tumor to limit definitely the rapidity of its growth.

The central giant-cell tumor usually remains small. It may enlarge relatively rapidly when it breaks through the thin cortical bone surrounding it, or when it breaks into a joint. The most malignant tumors may be small, for the patient may die of metastases before the tumor attains any size. The slowly growing, sclerosing sarcoma associated with definite bone formation and central chondrosarcoma may become large. Tumors situated peripherally as a rule grow faster than those situated centrally where growth and expansion are resisted by bone instead of soft tissues.

The findings upon palpation differ markedly The central giant-cell tumor as it grows, expands and destroys bone In some instances a definite parchmentlike crackling is found upon palpation. This same parchmentlike crackling is found in bone cysts. The roentgen findings should enable one to distinguish easily between the two lesions. The peripheral tumors arising from the periosteum or cortex are usually firmly attached to the underlying bone. As a rule, only a part of the circumference of the shaft is involved, so uninvolved bone may be palpated upon one part of the circumference In some instances the surface of the tumor is smooth in other instances it is irregular and nodular The irregular nodular surface is probably more frequently encountered than the smooth

In some tumors the signs of an aneurism may be found, and in the earlier surgical literature many of the tumors in which thrills were felt and bruits heard were spoken of as bone aneurisms. As pathologic studies have advanced, the use of the term "bone aneurism," has become more and more restricted. The pulsating bone tumors with thrills and bruits have well-defined histologic characteristics. These tumors occur most frequently in the spongy portion of long bones, the head of the tibia being probably involved most frequently Such tumors have been found in the bones of the pelvis, of the skull and of the foot (see Chap 9) The shafts of the long pipe bones

are but rarely affected, and then usually secondarily. Such tumors vary considerably in size. Pathologically these tumors resemble in most respects the central giant cell tumor, a bony shell being found. Parchmentlike crackling can usually be elicited. A number of different tumors, such as endotheliomas and hemangiomas, have been included under the term bone aneurism but this latter term should be replaced by the designation osteolytic sarcoma, which denotes their malignant character. These tumors resemble upon superficial histologic examination the central giant-cell tumor.

Localization

It is well to remember that tumors of bone, although they may occur in any part of the skeleton, have sites of predilection. Central giant-cell tumors, for example, are observed most frequently in the lower end of the radius, the upper end of the tibia and the lower end of the femur. Chondrosarcomas are probably found most frequently in the upper end of the humerus and lower femur. Other tumors have sites in which they most frequently develop. These facts cannot be used alone in making a differential diagnosis but should be remembered.

Systemic Reactions

The general condition of the patient may not be greatly disturbed, and a patient with a sarcoma may appear to be in good health. In advanced cases, however, the general health may be seriously affected. The cachexia so frequently seen in carcinoma may be absent in sarcoma unless ulceration with infection occurs. As the lesion develops, however, a marked anemia may be noted. The hemoglobin is reduced. Poikilocytosis is noted at times. Normoblasts and megaloblasts appear in some cases. The anemia does not differ in any way, however, from the severe secondary anemias due to other causes.

In some of the more rapidly growing cases a considerable elevation of temperature may be noted. I have seen a patient with a rapidly developing osteogenic sarcoma of the humerus who ran for some weeks a temperature as high as 103° F. Another patient with a sarcoma of the lower end of the femur which extended into the knee joint had a relatively high temperature. The rapid enlargement of the knee joint and the temperature suggested tuberculosis, but when the joint was aspirated, blood was found. These cases with temperature not infrequently simulate the clinical course of acute osteomyelitis. The clinical course is so much like that of osteomyelitis that differentiation may be impossible and a biopsy has to be made. Even differentiation by roentgen rays may be impossible. Endothelial myeloma of bone is accompanied by fever frequently and this tumor has probably been operated upon more often than any other under a mistaken diagnosis of acute osteomyelitis.

Metastases

Metastases indicate the malignant character of these tumors. Local recurrences are rare after mutilating operations. Lung metastases are the most common, and before an operation is performed, a careful clinical and roentgen examination of the chest should be made. I have performed a scapular amputation of the upper extremity for a sarcoma of the left humerus of almost two years standing which had been operated upon repeatedly. A careful roentgen examination of the chest was made before the amputation was performed and no evidences of metastases found. Within six weeks following the amputation, fluid was found in the chest and a roentgen examination revealed extensive metastases in both lungs. Chest and lung metastases may occur late. I have observed a patient with what appeared to me to be a central giant-cell tumor which was first curetted. Later a low amputation of the leg was performed because of recurrence in the marrow cavity above the site of the primary tumor. This patient died seven years after the amputa

tion and a bone-forming tumor was found in the left pleural cavity

Metastases by way of the blood stream are most common, so common, in fact, that not infrequently lymphatic metastases are not mentioned when the clinical course of sarcomas of bone is under discussion The smallest and probably the earliest sarcoma of bone that I have seen was associated with rapid involvement of the lymph nodes. This patient, a man of 30 years, had a Ewing's round-cell sarcoma of the lower end of the left femur In the roentgenogram definite erosion of bone could be seen. A biopsy was performed and a small tumor with the diameter of a half dollar was found above the internal condyle. Upon histologic examination this proved to be a small round-cell sarcoma. An amputation was performed. Within three months enlargement of the inguinal lymph nodes was noted. The lymph nodes along the external iliac and the aorta soon became enlarged and when death occurred the axillary and cervical lymph nodes were affected. Such extension is rare, but it should be remembered that lymphatic involvement does occur even in bone sarcomas. In some of the bone-forming tumors a thrombus forms in large veins, draining the tumor so that there may be a direct extension of the growth to the large veins of the thorax or into the cavity of the heart (see Chap 5)

Roentgenograms

With the introduction of x ray apparatus, the diagnosis of bone tumors became much more definite and the differentiation of the types of growths became possible. Roentgen examination undoubtedly furnishes more data than any other diagnostic method, but it should not be relied upon entirely to the exclusion of other methods. As has been previously stated, a tendency has developed during the past few years to neglect the clinical history and the physical examination. Both of these may reveal data of prime importance in differential diagnosis and in the determination of the nature of the lesion

The findings revealed by the x rays vary naturally with the location of the tumor and its mode of growth. The asymmetrical, globular shadow of the central giant-cell tumor differs markedly from the symmetrical expansion and the fusiform shadow of benign bone cyst. A tumor arising from the fibrous layer of the periosteum, which does not differ histologically from the fascial sarcoma, will destroy bone, giving rise to no reparative process. One has the impression that the bone has melted away The tumor arising from the cambium—osteogenic layer of the periosteum—destroys bone but is associated also with bone production, the newly formed bone being at right angles to the shaft, having a stalactite appearance. This appearance may however be closely simulated by inflammatory processes.

The difficulties in differential diagnosis may best be illustrated by discussing some of the lesions which give rise to the greatest difficulties.

Esmarch once said that he had seen in public and private practice forty cases of syphilis of bone in which a diagnosis of sarcoma had been made.

The difficulties of diagnosis are less, or are not encountered at all, when the lesion is multiple, as gummata frequently are. In the roentgenogram the differences between syphilis and sarcoma are quite marked. The subperiosteal gumma produces bone, and the calcium content of the bone involved is not lessened. It may even be increased. This finding is not absolutely positive as far as differential diagnosis is concerned, however for the sclerosing forms of sarcoma which have been seen most frequently in the Johns Hopkins Laboratory of Surgical Pathology in the upper end of the tibia produce a heavy shadow The shadow in the sclerosing form of sarcoma is quite different from that of the central gumma, which frequently suggests softening with cyst formation. The so-called periosteal spindle also suggests sarcoma, for this is not encountered in gum-

matous periostitis, the thickening of which is apt to be irregular Clinically the swelling in the soft parts is usually less marked in gummatous periostitis than it is in a sarcoma of approximately the same size. Longitudinal striations in the cortical bone, due to extension of the gummatous process to the Haversian canals is quite typical of syphilitic involvement.

The Wassermann reaction and the clinical findings are of prime importance in making a diagnosis. Since the introduction of the Wassermann reaction, the differential *diagnosis between syphilis and sarcoma of* bone is made with much greater certainty Yet there is no reason why a sarcoma of bone should not develop in a patient with syphilis.

The case about to be cited illustrates some of the difficulties which may arise.

This patient was seven years of age. Six months before being seen, she first complained of pain on the outer side of the fibula just above the junction of the upper and middle third. A slight injury preceded the development of the pain When seen by a surgeon, a swelling was noted over the site of the lesion, but the swelling in the soft parts was not as large as might have been suspected in a sarcoma. The skin covering the swelling did not have the peculiar bluish-red appearance so frequently associated with sarcomas. The child had some of the stigmata of syphilis. The shadow represented in Figure 1 has a fusiform shape. It has multiple, small, round cavities that do not resemble those of central giant-cell tumor or fibrous osteitis. Because no bone had formed beneath the periosteum above or below the shadow it was thought possible that this might be an endothelioma of bone. As this portion of the fibula could be resected without interfering much with the function of the leg, a resection was performed and this lesion proved to be a central gumma of the fibula which had destroyed a part of the cortex and periosteum without being associated with bone production.



Fig. 1 (No. 43020) Congenital syphilis of the bone with formation of a gumma suggesting in the roentgenogram a bone cyst or a Ewing's sarcoma. The periosteal reaction and perforation of the cortex are against bone cyst and in favor of sarcoma or inflammatory lesion. The Wassermann was 4 plus and the patient was aged 7

The teeth, facial appearance and Wassermann reaction were of prime importance in making a differential diagnosis in this case of congenital lues.

It may be extremely difficult to differen

tiate between a sarcoma of bone and non suppurative sclerosing osteomyelitis. A case illustrative of this difficulty is that reported from Garré's clinic in which a diag nosis of sarcoma was made by Ribbert from tissue removed at operation The patient was a boy seven years of age whose symptoms began with a limp A swelling then developed in the right thigh. The skin was not reddened and the tenderness found over an osteomyelitic focus was absent. In the roentgenogram the periosteum appeared raised. The contour of the bone was not sharp and the marrow cavity in the middle of the shaft was cloudy A periosteal sar coma was suspected and a biopsy made. When an incision was made soft, grayish masses infiltrating the bone were found A diagnosis of sarcoma was made after the tissue removed was examined



Fig 2. (No. 37748) A case of Garré's sclerosing osteomyelitis in the upper left tibia. The roentgenogram shows expansion of the bone and obscuring of the marrow cavity produced by new bone formation stimulated by low grade infection

Because the condition of the patient was regarded as hopeless, an amputation was not performed. After a year the patient appeared to be well. In the roentgenogram the bone appeared somewhat thickened and the surface fairly smooth. Medially there was a clear shadow 1 cm long Laterally there were many clear shadows the size of a penny

Garré described sclerosing osteomyelitis as an infectious osteomyelitis which leaves behind only expansion and thickening of the bone involved and is not associated with pus formation or the development of si nuses. The onset is acute at least in the majority of cases. High fever develops, the extremity involved becomes swollen and painful, and the bone enlarged. There is usually considerable involvement of the soft tissues, which would justify one in think

ing that pus would form. Instead, the infiltration of the soft parts gradually subsides, the fever falls, recovery gradually occurs and nothing remains but thickening of the differential diagnosis may be. The amount of bone destruction in this type of osteomyelitis is not as great as in the acutely developing sarcoma. In the sarcoma, although

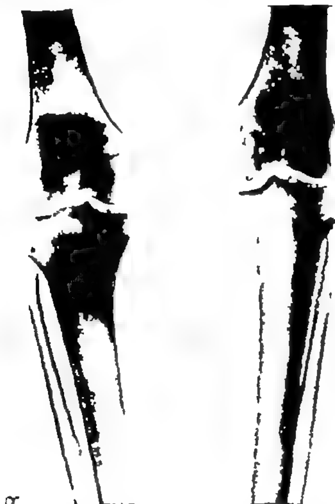


FIG. 3. (No. 40876) A case of sclerosing sarcoma in the upper right tibia. In this case there is a faint bone destruction accompanying new bone formation. The lesion is near the end of the bone and less diffuse than in the benign condition shown in Figure 2.

bone, the amount varying considerably in different cases. Garre came to the conclusion that in the sclerosing types of osteomyelitis which do not suppurate a sequestrum forms, but it is absorbed or encapsulated.

When one remembers that a sarcoma may develop acutely with severe pain and high fever that the skin covering it may be reddened and that pseudofluctuation may be elicited, one can see how difficult the there is bone formation this is accompanied by definite destruction of the cortical bone and an extension of the growth into the marrow cavity The periosteum in the sarcoma is raised on either side of the tumor the larger portion of which represents the oldest portion of the tumor In osteomyelitis of the sclerosing type the involvement is apt to be more extensive and the thickening more symmetrical.

As has already been indicated, however

the diagnosis may be difficult even after the tissue has been removed and examined. These difficulties merely indicate how much care must be exercised in the diagnosis of a lesion of bone. Certainly no mutilating operations should be performed until sections concerning which there can be no doubt have been examined. Occasionally some difficulty is encountered in differentiating between myositis ossificans and periosteal sarcoma. Myositis ossificans is seen most frequently in the brachialis anticus following posterior dislocations of both bones of the forearm which have been reduced promptly and correctly and in the vastus externus. This type of myositis ossifi

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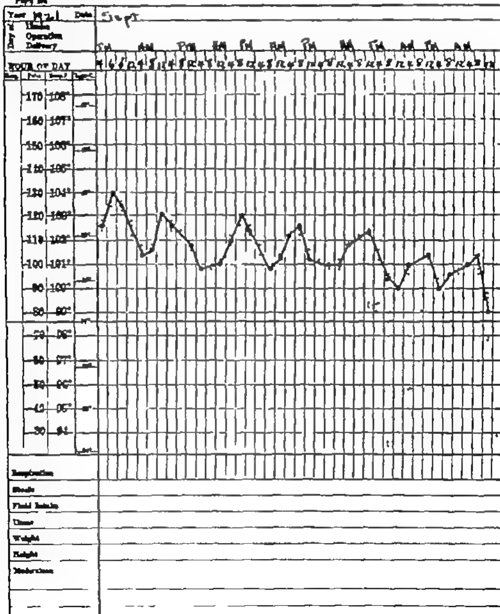


CHART 1. Temperature chart in a typical case of osteomyelitis.

cans is most common during the football season. The most common occurrence of myositis ossificans at these two sites may aid somewhat in the differential diagnosis.

In myositis ossificans the base of the shadow resting on the bone is usually smaller

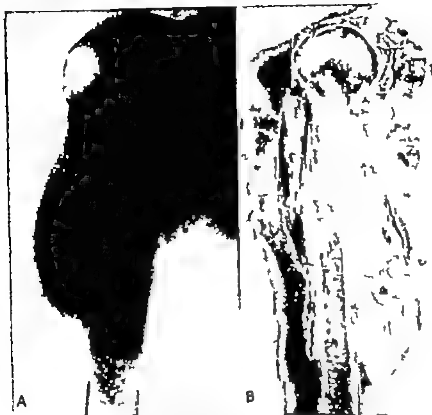


FIG. 4. (No. 36014) Roentgenogram and gross specimen of case diagnosed as myositis ossificans but terminating in metastases and death.

than the main shadow which seems to be attached by a pedicle. The periosteum on either side of the attachment is not raised. The bone is usually laid down parallel to the shaft rather than at right angles, and the shadow has what has been described as the dotted veil appearance.

The following case, studied and reported by Dr T R. Chambers of Baltimore, will illustrate the difficulties occasionally encountered in differentiation between myositis ossificans and periosteal sarcoma.

The patient, a male aged 28 years, while helping to lift an automobile from the mud felt a sudden, sharp pain in the upper portion of his right arm and shoulder The following day the arm was tender also the shoulder and the muscles of the neck on the right side. Some swelling without discoloration was noted, and hot applications were advised by his physician On April 7 1923 a marked swelling was found on the outer side of the right arm over the prominence and insertion of the deltoid. The skin covering this appeared normal neither dilated nor enlarged veins were noted. The mass was indurated, almost bony in consistency smooth, not lobulated. It seemed to be in the deltoid muscle. The skin could be moved over the mass and the growth on the humerus. Roentgenograms taken at this time showed a definite bone-forming mass on the outer side of the right humerus. This was thought to have followed stripping of the periosteum at the insertion of the deltoid, resulting from indirect violence the month before

The patient was advised to stop work,

apply hot applications and keep his arm in a sling. Notwithstanding the fact that the Wassermann was negative, 45 grains of potassium iodide were administered each day The patient remained away from work two months and then returned because of economic reasons.

He reported again in October 1923 because of pain and an increase in the size of the mass. At this time seven months after the injury the mass was larger felt bony and seemed to be extending around the shaft of the humerus. It was firmly attached to the shaft on the outer side, but the tips of the fingers could be made to dip under the mass on the posterior and inner side The mass seemed to be pedunculated and attached to the humerus at one point.

A diagnosis of myositis ossificans was made. During September 1924, the mass, which had been enlarging slowly began to grow rapidly and increased 4 cm. in size in four weeks. Pain became more severe and could not be controlled by codein. Because of the increase in size, an operation was decided upon.

During the operation a large mass was exposed. This was reddish-gray in color and not encapsulated. There was no line of cleavage. Considerable periosteum was removed and some cortical bone curetted away The specimens were examined by several pathologists and a diagnosis of myositis ossificans made. There were no evidences of malignant disease. Bone, cartilage, muscle and connective tissue were irregularly distributed through the tissue

Two months later—the patient having been relieved of his symptoms to a considerable extent—some induration of the muscle could be made out. A shadow could be seen in the roentgenogram Radium therapy was instituted and a wrist drop which was present improved promptly The growth increased rapidly in size and extended up toward the shoulder joint. The shoulder joint became ankylosed. The patient was free of pain, but the mass continued to grow larger An amputation was advised.

One and one-half years after amputation there were no evidences of recurrence. The patient looked well.

He was readmitted to the hospital on April 19 1929 He was hoarse and short of breath. He had enlarged cervical lymph nodes of bony hardness, and a roentgen examination revealed a mass in the upper right chest and another mass in the left chest. He died shortly after entering the hospital.

The autopsy revealed bony masses in the right and left chests. The right lung with the tumor was about twice as large as normal and weighed considerably more than the left lung and tumor Bony metastases were also found in the cervical lymph nodes on the right side.

The following note is found in the history which was made on November 21 1929 No cells are seen from which a diagnosis of malignancy can be made. However the newly formed bone is much less orderly than in sections of myositis ossificans. The trabeculae are blotchy and the tissue filling the cancellous spaces of the new bone and about its margins in many places is richer in spindle cells, and where there is considerable intercellular substance there is less tendency to form bone marrow than in myositis ossificans.

The clinical history was of prime importance in making a diagnosis in this case. The lesion was progressive from the onset The course might have been modified by the first operation, for myositis ossificans is apt to be made worse by operation but the progressive character of this lesion associated with some bone destruction suggests that this is an ossifying periosteal sarcoma.

The next patient, a boy eight years old, presented a difficult diagnostic problem. About the first of June, 1931, he began to complain of some pain in his right arm. Some weeks prior to this he had fallen and struck his shoulder on a water spigot. The pain in the arm continued and on June 16

n incision was made over the supposedly osteomyelitic focus. It is recorded in the history that about 1½ ounces of pus escaped. The fever which the child had soon subsided and in a week he was dismissed from the hospital. He soon began to have fever again, the pain in the arm increased and on July 8 another roentgen examination revealed considerable periosteal reaction (Fig. 5) The old incision was reopened and lengthened, some necrotic tissue removed and pus released. On August 8 the incision was again opened, with the idea of removing a sequestrum At this time a large amount of soft tissue was found. This appeared malignant. A diagnosis of Ewing's tumor was made at that time.



FIG. 5 (No 45830) A Ewing's tumor in the upper humerus producing bone sclerosis with secondary bone destruction The tumor had been explored twice previously and pus reported at both operations. The sections, however show typical Ewing's sarcoma.

The general reaction in this type of sarcoma is emphasized in Chapter 17 In 28 cases in which accurate temperature curves

could be had the temperature ranged between 99° and 104° F., the average being 100. Fever was more commonly observed late in the disease after metastases had formed, but it appeared early in the clinical course of the disease in 30 per cent of the cases. Associated with the fever was a slight albuminuria in many cases. The blood changes were variable, ranging from the normal to a secondary anemia. In some cases a relative leukopenia was noted, in others a marked leucocytosis.

Roentgen examination in these cases indicates that *Ewing's tumor is not always* primarily destructive of bone. In early cases, the first evidence of neoplastic infiltration may be an increased density of the bone affected. The degree of bone change in these cases with little periosteal involvement would suggest a neoplasm, while the clinical history suggested an acute osteomyelitis.

Many other cases might be cited to indicate the necessity of careful clinical and roentgen studies in the diagnosis of these tumors and the importance of knowing the clinical course of the disease so that the typical and atypical cases may be recognized.

Ossifying hematomas may rarely cause some difficulties in diagnosis. The ecchymosis following the injury in such a case is of importance, for slight trauma, if there is a relation between trauma and tumor formation, precedes the discovery of sarcoma. Severe trauma is not usually associated with the development of tumor growths. The ossifying tumor also reaches its maximum size quickly and then recedes. There are no changes in the skin such as are frequently seen in sarcoma.

Gout may destroy bone and simulate in some ways a bone tumor but the other stigmata of gout will usually be found upon examination. Subperiosteal hemorrhages occurring in scurvy should not cause much *difficulty in making a diagnosis. The* definite localization of the lesion in the diaphysis, its extension around the shaft, sharp borders and the changes in the epiphyseal zone are sufficient data upon which to make the diagnosis.

Many other difficulties encountered in making the diagnosis of tumors of bone might be cited. The earlier the lesion comes under observation, the greater the difficulties. It is only by the correlation of the different procedures and the proper evaluation of their significance that a correct diagnosis can be made.

In any case in which a mutilating operation is to be performed, a biopsy should be made. If there is any doubt whatsoever final judgment should be reserved until the best section that can be prepared is carefully and competently studied.

RULES OF DIAGNOSTIC AND THERAPEUTIC PROCEDURE FOR BONE LESIONS

Joseph Colt Bloodgood, M.D

No matter how complete the physical examination and the laboratory studies, there must be just as careful an investigation of the history of the case. This history is not only valuable for diagnosis but is always of increasing value when large numbers of cases are investigated in the search for data on which to base working rules for diagnosis and treatment and a more comprehensive *history of the disease itself*

Any member of the medical profession, whether connected with a hospital or not, can assemble all the laboratory investigations, can make and describe the physical examination, and can obtain and write out the history. If he is not able to interpret the roentgenograms, the laboratory findings and the information obtained by physical examination and from the history, he can *get expert advice by sending the roent*

gen films and the data recorded to a recog nized medical center

RULES OF PROCEDURE

1 Do not perform an operation as an emergency or to obtain a piece of tissue for microscopic study (biopsy) unless there is definite evidence of an acute infection with or without abscess that demands immediate drainage.

2. Do not perform an operation or a bi opsy until the history physical examination and all the laboratory investigations are assembled and carefully studied. When the roentgenogram is very indicative of malig nant disease, there is no objection to giving deep roentgen therapy while waiting

3. When the clinical and laboratory in vestigations are finished and doubt exists as to the diagnosis and help is desired, the roentgen films and the clinical and labora tory data should be referred to the clinic selected as consultant before biopsy While waiting there is no harm in continuing deep roentgen therapy

4. Do not mention amputation or any mutilating operation until the investigation has been completed and it is quite certain that amputation or resection may be necessary

5. Mikulicz years ago, before 1900 ad vised the most radical resection which left a limb with function (although such func tion was not as good as that of an artificial limb) because he found that when amputa tion was suggested, the patient refused further treatment. When amputation is the treatment of necessity for malignant disease of bone, the most important thing is to obtain permission to amputate the limb Responsibility does not end with suggesting amputation. The physician s science may be successful in interpreting the data in favor of this radical procedure, but his art is a failure if the patient refuses treatment.

6. Biopsy may have to be performed to settle the diagnosis and treatment even when the roentgenograms have been seen and all the data carefully studied by one or more students of large experience. Then this dilemma may be encountered the pa tient may be in a clinic in which the pathol ogist responsible for the diagnosis in the operating room is not familiar with or suffi ciently experienced in the differential diag nosis of the microscopic appearance of the various tumors and diseases of bone. The surgeon may be perfectly capable of per forming the operation of choice or necessity but when the consultants are unable to make the diagnosis from the roentgenograms and the local pathologist is not ready to assume the responsibility the question arises "Shall the patient be sent to the nearest clinic in which there is a trained pathologist for this diagnosis?" This often adds considerably to the patient s expense. When a study is made of the sarcomas of bone of which there are records in the laboratory in the cases in which the patients have lived five or more years after opera tion, it is found that in almost 50 per cent there has been a biopsy with an interval of time between the biopsy and the amputa tion or resection. Therefore, the consultant who advises from roentgen and other data should advise how the biopsy can be per formed with the least element of danger of disseminating malignant disease. A microscopic report should be obtained on the material secured by biopsy in the time that it takes the mail to reach the diagnostic laboratory and a telegram giving the diag nosis to return.

This is a very important statement and is based upon a very large amount of material over a number of years. In 1913, in the writer s own experience, two successful amputations were performed—one for sar coma of the lower end of the femur the other for sarcoma of the upper end of the tibia. Both tumors were osteogenic sarcoma, both patients are living and free from dis ease today more than twenty years later In the case of the sarcoma of the tibia, the roentgenograms were submitted to a num ber of roentgenologists who differed as to the diagnosis between a benign and a ma

lignant disease. A number of pathologists who had examined the sections from a piece obtained agreed that it was osteogenic sar coma. This case has been accepted as sar coma by the Registry of Bone Tumors of the American College of Surgeons. The in terval of time between the biopsy and the amputation was two weeks. The biopsy was performed with the knife and chisel with out cautery or any chemical disinfection.

In the second case the amputation was performed on roentgen diagnosis. The ratio of cases cured by amputation after biopsy to cases cured by amputation without bi opsy has remained about the same in the writer s subsequent experience which now includes 68 five-year cures.

There is a case of Ewing s sarcoma of the lower end of the fibula upon which biopsy was performed and followed by roentgen treatment. The treatment was clinically successful In the roentgenogram the bone appears restored to almost normal. The limb was saved. The patient lived four years and died of metastases to the lungs.

In a second case, there were two partial removals of a lesion of the tibia. The sec tions revealed Ewing s sarcoma. The treat ment was radium without resection. The wounds healed. The roentgen plates showed restoration to almost normal. The patient is living today more than ten years since the treatment. There is another case of sar coma of the tibia of the osteogenic type. There were two partial removals. Then, after a recurrence, the involved tibia was resected and a piece of fibula transplanted. The patient is apparently free from disease four years later

An added advantage of biopsy is that, in the great majority of the cases, it allows the patient to remain at home. The physi cian studying the case can get the best help first from the roentgenograms and later from the section and can then proceed according to advice, apparently with good results.

7 More and more people are learning the value of immediate roentgen examination after an injury even when there is no fracture. They have a roentgenogram taken the moment pain or tenderness or swelling or loss of function in a limb is observed. This enlightenment of the public in his locality should be encouraged by the practi tioner The roentgenologist must be prepared to see benign and malignant tumors and diseases of bone in their earliest stages. The roentgenogram, instead of becoming more familiar will become less familiar In this clinic, where each week more lesions of bone are being seen than ever before, a greater number of cases difficult to diag nose are being encountered, not only in the roentgenograms, but also in the frozen sections

This experience emphasizes the impor tance of definite rules of procedure, work ing rules for diagnosis and treatment, which will give patients in the earliest stage of disease the best assurance of a cure with the least danger of an unnecessary resec tion or amputation.

8 When irradiation is chosen for the first treatment for sarcoma of bone, with every evidence of operability—resection or amputation—it should be given up if results are not seen promptly say in two or three weeks. When the situation and size of the malignant disease render it inoperable, ir radiation may be pushed to the limit. At the present time irradiation with x-ray or radium for sarcoma of bone cannot com pete with amputation or resection. How ever it is the only treatment when the con dition is inoperable

For example, a patient, aged 64, with a central destructive lesion of the upper end of the humerus was first seen when the bone shell was intact. It was the only bone lesion found in the roentgenograms. There was nothing to suggest that it was metastatic. The probability was that it was a giant-cell tumor It could have been any type of primary sarcoma or a metastatic tumor There was more loss of function and more pain than is usually observed in the giant cell tumor In this case, under roentgen

therapy by a most competent and experienced roentgenologist the pain was not relieved, the loss of function grew worse and the bone shell disappeared, but the tumor did not increase in size This treatment was carried on for one year When the patient came under observation he was taking 4 grains (0.26 Gm.) of morphine a day and was pathetically miserable mentally and physically The upper end of the humerus was then resected under rectal avertin anesthesia. The tumor proved to be a metastatic hypernephroma There were no signs or symptoms of a primary tumor The patient was almost completely relieved of pain and within two weeks was getting along without morphine He lived in relative comfort for four years and died with metastases to the liver Undoubtedly the tumor growth was somewhat checked by irradiation, but its continued use in this case over such a long period was a mistake In a second case of osteogenic chondromyxosarcoma, the patient not only lost his limb but will ultimately lose his life because deep roentgen therapy was pushed for more than a year in spite of the fact that the tumor grew larger the roentgenogram showed increasing bone destruction and the patient experienced increasing discomfort. Because of soft part infiltration it was necessary to do a shoulder joint amputation. This was not extended to the shoulder girdle, because beadlike strands could be seen passing through the tumor into the axilla and into the intercostal muscle and frozen sections of the intercostal muscle showed the characteristic tumor cells. This patient now has palpable tumors in the stump and chest wall which are being treated with radium. He is quite comfortable The roentgenogram of the chest shows no metastasis.

Those who have studied the material in the laboratory see no objection to trying irradiation in bone lesions in which there is suspicion of malignancy in the roentgenogram. When the local disease is inoperable or is a metastatic one the irradiation therapy should be continued, but when the disease is operable no risk should be run of allowing it to become inoperable. No evidence exists that roentgen therapy increases the danger of metastases, nor as yet is there any evidence that it prevents metastases.

9 In regard to irradiation of the benign giant-cell tumor of the epiphysis, the writer has found that the younger generation of students of tumors and diseases of bone who have studied the actual results of roentgen treatment of the giant-cell tumor and compared them critically with the results of proper curetting and resection when indicated, are coming to the conclusion that curetting is much more economical of time gives a better result as to function and has no greater percentage of recurrences. It also offers opportunity for microscopic diagnosis. Ultimately every giant-cell tumor should be curetted, except now and then when there is a rare malignant change associated with a benign giant-cell tumor or a malignant tumor masquerading under the picture of a benign giant-cell tumor This should occur in less than 1 per cent of the cases.

When the roentgen therapy in a giant cell tumor is pushed, there is risk of overlooking a possible malignant tumor or even of producing one. There seems no question, however that irradiation has checked the growth and has permanently cured cases of benign giant-cell tumor

10 Palpation should never be neglected. Now and then it is absolutely diagnostic Some time ago the writer palpated the left upper arm and the area over the scapula in a man aged 24 Fluctuation favored abscess, and two definite red spots in the skin over the posterior side of the upper arm were in the position of the usual pointing of pus from an osteomyelitic or tuberculous area in the body of the scapula. These points have been known for more than 40 years. The writer reviewed them in Progressive Medicine about 30 years ago Cases of this kind are less frequently seen today This patient had been roentgenographed at

his home in a state 1,000 miles away and a brief history was sent. Most of the writer's associates diagnosed sarcoma, but in a central area of destroyed bone there was the picture of a sequestrum. The bone surrounding it presented the picture of a sclerosing sarcoma. In the roentgenogram, sclerosing sarcoma cannot always be differentiated from sclerosing osteomyelitis (Garré type) *Nothing* was said about palpation in the history Further data were written for but the patient went to another clinic before the letter was received. After careful roentgen study at the second clinic, irradiation with radium was decided upon. The patient again changed his mind and entered the writer's clinic. Palpation settled the diagnosis Sarcoma with abscess has been found to be practically nonexistent. The abscess over the scapula extending to the arm was not appreciated elsewhere as a definite clinical sign of osteomyelitis or tuberculosis.

Less and less today are the clinical features of benign and malignant tumors of bone and of diseases of bone helpful in the diagnosis, but they should never be neglected. In former years, when malignant disease could be recognized clinically there were no cures. For many years tuberculosis *and osteomyelitis were easily recognized* without roentgen examination. Palpation of new bone formation suggesting exostosis, periostitis or ossifying myositis no longer yields a positive diagnosis. Some bone-forming periosteal sarcomas feel like a benign lesion. The palpation of a spindle-shaped tumor about the shaft of a bone, which is given as a positive diagnostic sign of sarcoma in all the old literature and textbooks, can no longer be depended upon. Nonsuppurative osteomyelitis of the Garré type may also produce it.

In spite of this, palpation should never be neglected, and a complete physical examination should be performed.

11 Roentgenograms of the affected and also of the opposite unaffected bone should be made. The less evident the bone changes in the affected area, the more important is a roentgenogram of the opposite part. Some years ago an experienced surgeon and roentgenologist took a roentgenogram of the upper end of the right tibia, because the patient, a child, aged 10 complained of a painful bump over the tubercle of the tibia. It had been present but a few weeks. The parents were told that a biopsy should be *performed and if a frozen section revealed* sarcoma, an amputation should be done. The parents followed von Mikulicz's rule—they left the clinic and went to another Fortunately the writer was quite familiar with the Schlatter-Osgood disease in this epiphyseal area, but he had observed at that time two cases of sclerosing sarcoma of the upper end of the tibia which exhibited the clinical picture of the Schlatter Osgood disease. It had been possible to recognize the sclerosing sarcoma by comparing the roentgenogram with that of the opposite side in early cases. Therefore, in *this case, films were made of both tibiae.* They both looked alike, although the right area was tender and the tubercle more prominent. There was no evidence of sclerosis on either side. The irregularities were all in the epiphyseal line and were quite characteristic of the changes common in *this part of the bone at this age This patient* is free from trouble today without radical treatment 15 years after the first examination.

Multiple exostoses and other types of multiple lesions may be brought out by taking two roentgenograms. The comparison also facilitates the detection of the most minute areas of bone formation and bone destruction.

12. A roentgenogram of the chest should never be neglected. It is not always possible to differentiate calcified, healed tuberculosis from metastasis. Every individual at any age, should have a roentgen examination of the chest from time to time, and if there is a bone lesion, this adds to the importance of that study One patient under observation had multiple pigmented moles

none appeared malignant. There were no symptoms to suggest a roentgenogram of the chest. Pain in the region of the coccyx and the sacrum indicated a roentgenogram there. The chest plate was made as a routine procedure and showed many metastases, while the roentgenogram of the painful area in the sacral zone was negative. It was at least known that he had a hopeless disease no matter where the primary lesion may have been. In another instance, a patient was being treated for anemia; the blood examination even suggested pernicious anemia. There were no symptoms referable to the chest. Suddenly he had a hemoptysis. Then a roentgenogram revealed multiple metastases, and the autopsy a hypernephroma.

13. Roentgen films of the teeth and a search for foci of infection should be made. In children, a roentgenogram records the presence or absence of nonerupted teeth and whether they are misplaced. In adults, it pictures the root abscess, if present, and allows the tooth to be extracted before symptoms of general infection set in. The neglect of taking roentgenograms of the teeth in lesions of the bone often leads to incorrect diagnosis and even incorrect treatment. For example, a man of 30 limps, has a painful spot below the great trochanter of the right hip; feels a hard mass there. A roentgenogram is taken of this part only. It shows bone formation and bone destruction over a small area of the periosteum below the trochanter. A little spicule of bone in the soft parts is not observed—it is about 3 mm. long. Hip-joint amputation had been advised. However, abscessed teeth and infected tonsils were found. Immediately after their removal the pain and tenderness and the lump disappeared. Later operation was done under procaine and the sequestrum removed and pyogenic organisms were found in coverslips and cultures. This excluded malignant disease. As the patient is free from symptoms today without radical treatment, the diagnosis must have been correct.

It is unnecessary to repeat many examples of this kind.

Search should be made for foci of infection everywhere. Second in importance to filming the teeth, are examinations of the tonsils, nasopharynx and sinuses. Boils should be looked for or a history of boils. In many cases of osteomyelitis this has been observed, rarely if ever in sarcoma. The prostate may reveal cancer or infection. Metastases to the bone from cancer of the prostate are much more frequent than osteomyelitis from infection in the prostate.

Finding definite foci of infection does not exclude a primary benign or malignant tumor of bone, nor a metastatic osseous lesion. The reverse is also true—osteomyelitis or tuberculosis may be present even when signs of a focus elsewhere are absent.

In cases of doubt in which foci of infection are found, the irradiation of the bone lesion may proceed while the foci of infection are being eliminated.

14. In searching for multiple lesions in the skeleton, there should always be a roentgenogram of the pelvis, the chest and a lateral view of the skull. When the lesion is in the tibia, the finding of other evidences of Paget's disease in the pelvis and skull is helpful, but this does not exclude the possibility that sarcoma has developed upon a Paget's osteitis of the tibia. Codman, of Boston, from his studies, has published the opinion that sarcoma and Paget's disease are not uncommon after 50 years of age. On the other hand, metastatic carcinoma may be present in the Paget lesion and very difficult to distinguish. In a case in the writer's experience, the tibia, pelvis and skull were the seat of Paget's disease. The patient complained chiefly of intense pain in the skull—a clinical feature usually absent in Paget's disease. Both breasts had been removed more than 10 years before. The pathologic diagnosis on the breast tissue could not be obtained. A piece was removed from the skull and it revealed metastatic carcinoma. Dr. Ginsberg, of New York, kept this patient comfortable for a number of years

and has reported this observation in the literature.

Again and again it is the roentgenogram of the pelvis that has pictured most definitely the metastatic lesion It will also depict the lumbar spine, a favorite site for metastases to bone

15 Repeated roentgenograms should be made. Not only should every attempt be made by the roentgenologist or his technician to take good pictures but in obscure cases to take them in all possible directions. The writer once examined about 25 films of the right knee taken over a period of some six months, during which time no picture had been taken of the opposite knee. In each instance only an anteroposterior and lateral view of the affected right knee had been made In the first place the films were not clear The picture suggested tuberculosis, which agreed with the clinical picture. What changes there were became more evident when compared with the normal left knee. It could be seen that the lesion was confined to the lower end of the femur that the patella and tibia were free from disease except osteoporosis due to nonuse There was a definite area of bone destruction in the outer condyle of the femur in the anteroposterior view which could be explained by tuberculosis Nevertheless, there was something obscure in the roentgenogram, and it is known that sarcoma may be associated with the clinical picture of the so-called "white swelling of the knee"

Finally a lateral view in a new direction was obtained, which revealed a small area of periosteal bone formation rarely present in tubercular osteomyelitis and sufficiently suggestive of sarcoma to justify an exploration for biopsy Now this case had been under observation for more than six months.

The patient had been carefully examined in a number of well known clinics. The only diagnosis made was negative for sarcoma." During this time the unaffected knee had never been roentgenographed there had been no treatment but rest and this not associated with the proper environment for tuberculosis exploration for biopsy or irradiation had not been suggested. Today there is no justification for such unnecessary delay The diagnosis can and should be made at once Sarcoma must always be thought of and when this is situated in an operable bone, biopsy for diagnosis and immediate treatment should never be delayed when irradiation fails to help at once The majority of patients and their families are timid. All fear to face resection or amputation At the present time, these two operative procedures offer more promise of cure than any other method. Unnecessary delay increases the chances of metastases, decreases the chances of resection. This, in the upper extremity is disastrous, because experience teaches that when amputation must be done to remove a sarcoma of the bones of the upper extremity the patients die

16 Blood Wassermann tests should be made Syphilitic lesions of bone are becoming less frequent because of the universal employment of the blood test and the immediate intravenous treatment. The majority of roentgenologists, surgeons and pathologists, especially those who have served in the army are familiar with the clinical or roentgen manifestations of syphilis of bone. But there is no excuse for proceeding to biopsy or the operative treatment of a bone lesion until the report on the Wassermann reaction has been received. Two examples of syphilitic lesions of the fibula were seen by the writer both treated in the same clinic. In both, the lesion of the fibula was resected for sarcoma (one after biopsy without waiting for the Wassermann report, which was positive in both instances) In the writer's opinion, resection was the best procedure for the most rapid correction and local cure of the disease. In both patients there is good function. Nevertheless, nothing was gained by operating one day earlier In the first place, a rare opportunity was lost to see the effect of intravenous treatment on the bone lesion hav

ing all the appearances of an ossifying osteogenic sarcoma.

In the writer's first studies of bone tumors there was no Wassermann test to render assistance. As a rule, syphilitic periostitis was diagnosed because of the multiplicity of the lesions, because of the localization in the clavicles, sternoclavicular joints and tibiæ. In a few instances, diagnosis was made at biopsy. Most patients with painful, tender tibiæ were given iodide of potassium and mercury. After the advent of the roentgen technic and before the Wassermann, there was nothing specific in the roentgen picture of syphilitic periostitis. The writer's records show that the single lesions, which were very rare, were explored and the inflammatory lesion properly diagnosed, and there were no amputations for syphilitic periostitis. Then came the Wassermann reaction, which was often neglected and frequently inaccurate. During this period, in spite of negative Wassermanns, the writer employed antisyphilitic treatment just as preliminary irradiation is now employed. Four patients are recorded in whom sarcoma was diagnosed from the roentgenogram; they have remained well following antisyphilitic treatment. One of these patients was involved in a rather dramatic incident occurring many years ago. The writer first met him when giving a clinic at the annual postgraduate meeting of a medical school connected with a university. The patient's lesion was in the tibia and the roentgenogram suggested a sarcoma, the Wassermann was reported negative. The patient had consented to amputation, even wanted the amputation. The audience was enthusiastically in favor of an amputation. Great difficulty was encountered in persuading the patient and his medical advisers to postpone the operation. This patient is well today and has good function of the leg.

The other observation is equally dramatic. The father of the writer's resident surgeon was being shaved by his barber one day when the barber told him that his son was to have his arm removed for cancer the next day. The barber was persuaded to take his boy to Baltimore. No Wassermann test had been made. The blood tests of both father and son, and later of all the family, except the mother, were positive. The roentgenogram showed involvement of the shaft and periosteum. It was difficult if not impossible to differentiate between osteomyelitis and sarcoma. A piece had been excised for diagnosis, and the lymphoid-cell granulation tissue of syphilis interpreted as small round-cell sarcoma. As the boy was not improving under Coley's serum, amputation was decided upon. Under intravenous treatment the boy rapidly recovered, the sinuses healed.

Today, the Wassermann reports have few if any elements of error. Sufficient experience with the intravenous therapy has shown that when the bone lesion is syphilitic, almost immediate improvement is observed. Within ten days or two weeks the therapeutic test will be quite certain.

Antisyphilitic treatment may accompany irradiation with roentgen rays and radium. In recent years, the mistake made was usually neglecting to take a blood Wassermann or proceeding without waiting for a report.

When the lesion is in the spine, it is important to perform a neurologic examination and to include a study of the spinal fluid. A positive Wassermann reaction on the spinal fluid may be diagnostic in a Charcot's lesion of the spine.

17. Blood counts should be made. In pyogenic osteomyelitis the total leukocytes are usually higher than in sarcoma, and there is an increase in the polymorphic leukocytes. In sclerosing, nonsuppurating osteomyelitis of Garré, there is usually no diagnostic change in the leukocytes. Quite frequently, the blood count has been helpful in diagnosing subacute osteomyelitis before the demonstration of a *sequestrum* or pus. The finding, at the exploratory incision, of pus or sequestrum practically excludes sarcoma, if there has been no previous operation and no irradiation producing

a deep burn. The writer has never observed a bone lesion associated with leukemia, but *when the white count is above 25 000 and* multiple bone lesions are present, chloroma is to be suspected. Extreme anemia is suggestive of malignancy with metastases.

18. Urine should be tested for Bence-Jones bodies. As a matter of fact, today the finding of Bence-Jones bodies in the urine is so unusual or so seldom thought of that even in multiple myeloma, it has not been very helpful. In fact, Bence-Jones bodies may be rarely present in benign lesions. Some years ago, these bodies were found in the urine of a patient with a lesion of the rib which, in the roentgenogram, was more like osteomyelitis than multiple myeloma. At operation, inflammatory tissue was found and at first the granulation tissue was not unlike that in multiple myeloma. The lesion had followed some months after typhoid fever Staphylococci were cultured from the granulation tissue The Bence-Jones bodies disappeared after operation The wound healed. No other lesion of the skeleton appeared. *The patient is clinically well today*

The writer's first experience with Bence Jones bodies was very disappointing, and produced a great deal of personal chagrin. He had written in his reviews of the literature in Progressive Medicine that no opera*tion should be performed upon a bone tu*mor without an examination of the urine for these bodies. This was many years ago Then his friend, Dr George W Crile, brought to his attention the roentgenograms of the outer third of the clavicle, which showed an expanding tumor of central origin with almost complete destruction of the bone shell in places. The bulging could easily be palpated. The patient was too old for a bone cyst, except the rare latent one.

At that time the writer knew more of giant-cell tumors of the clavicle than of any other lesion. The destruction of the bone shell caused suspicion of a malignant lesion. Roentgenograms of the entire skeleton were negative. The patient was in good health. His attention had been called to his shoulder by pain The condition was diagnosed rheumatism by the physical director of the *gymnasium where he took his* noon exercise, and this physical director gave him massage. As there was no relief Dr Crile was called in for consultation. The roentgenogram was shown to the entire Society of Clinical Surgery

The writer missed the opportunity of suggesting an examination of the urine for Bence-Jones bodies. Resection was performed because the destruction of the bone shell suggested malignancy in addition, the loss of the bone would not be mutilating

Dr Howard, the pathologist connected with Crile's clinic at the Lakeside Hospital, made an immediate frozen section and diagnosed multiple myeloma. He then catheterized the bladder before the patient recovered from the anesthesia and found Bence-Jones bodies. Gradually multiple lesions developed with a fatal termination. It is a good rule to examine the urine for Bence-Jones bodies in all lesions of bone.

19 A test for blood sugar should be *made. Even when the urine is negative for* sugar it is wiser when the patient is an adult, to know the blood sugar No relation has been observed between diabetes and bone lesions. But, if there is to be extensive operation, especially resection with bone *transplantation, it is best to have the pa*tient prepared, if there is high blood sugar with or without sugar in the urine.

20 Temperature should be carefully checked. It is a mistake to neglect rectal temperature. In the earliest stages of sar*coma, when the lesion is small, fever is* rarely observed, while fever in osteomyelitis may be present in any stage of a restricted or extensive lesion. On a few occasions, slight fever and leukocytosis have been helpful in indicating osteomyelitis.

21 The blood chemistry should be tested routinely Routine blood chemistry should always be a part of a diagnostic or preoperative investigation, particularly in multiple lesions of the skeleton. The most definite disturbance in the serum calcium and phos-

phorus should accompany rickets, von Recklinghausen's disease, osteomalacia and ununited fracture. In multiple myeloma the blood proteins may be raised to twice their normal value (Chap. 18) and in lesions of the small bones caused by gout the uric acid is increased. The blood phosphatase is increased in Paget's osteitis deformans. It may also be raised in osteogenic sarcoma or benign giant-cell tumor but the extremely high values found in Paget's disease are diagnostic. Hormone determinations performed on the tumor tissue rather than the blood are of interest. The pituitary sex hormones and growth hormones may be found in osteogenic sarcoma, and extraction of benign giant-cell tumor for parathormone has been carried out in a few cases with positive results in this laboratory

Irrespective of the findings of blood chemistry in all benign diseases of bone associated with bone destruction, it is a good plan to give a bone-forming diet, both as a preoperative and postoperative therapeutic measure. This diet has been found of special value in ununited fracture, but so far I have been unable to observe definitely its importance in bone cysts or after operation for giant-cell tumor in which the disease has been curetted and the bone shell left behind. As a matter of fact, estimations of blood chemistry are rare, except in recent cases.

22. A metabolism test should be made. This is becoming almost routine in a thorough diagnostic investigation When there is evidence of a single or multiple lesion of the skeleton, the metabolism test will be helpful in suggesting certain rare bone dystrophies of unknown origin. Hypothyroidism has been found associated with Paget's disease of bone and in osseous changes in cretinism. Delayed union of the epiphyses is also characteristic of this condition

PART ONE

Embryogenesis of Bone and Its Relation to Skeletal Tumors

1

Embryogenesis of Bone and Its Relation to Skeletal Tumors

EMBRYONIC PROCESSES IN FORMATION OF BONE TUMORS

The variety of tumors of the bone is dependent not solely upon the number of different structural elements, such as connective tissue, cartilage and bone comprising the skeleton, but also upon the developmental steps necessary for these component tissues to reach the adult state. Most neoplasms of bone are associated with phases of osteogenesis, and it is in connection with such transitions in growth that the primary tumors of the skeleton arise. These tumors are commonly classed as osseous in origin. New growths springing from the marrow the vessels, and the overlying fibrous tissue and invading bone from without also occur but these are less common and form a supplementary group classed as tumors of nonosseus origin (Table 1)

SUMMARY OF EMBRYOGENESIS

It has now been well established that the development of the human skeleton does not reach a final static form in early adulthood, as was formerly taught. Instead, there persists at various places throughout life foci of growth where transitional forms between the development of different tissues persist, each transition presenting a possibility for tumor formation. These developmental foci, which carry with them a neoplastic liability are distributed in accordance with prearranged structural patterns. The majority of osteogenic neoplasms occur at sites which correspond to such normal

TABLE 1 CLASSIFICATION OF BONE TUMORS

A. Tumors of Osseous Origin		
Cartilaginous	*Osseous*	*Resorptive*
Osteochondroma (solitary and multiple)	Osteomas and ossifying fibromas of skull and jaws	Bone cyst
Chondroma	Osteoid osteoma	Diffuse osteitis fibrosa (parathyroidism)
Chondroblastoma, benign and malignant	Osteogenic sarcoma, sclerosing and osteolytic	Fibrous dysplasia, polyosteotic or monosteotic
Chondrosarcoma, primary or secondary	Parosteal ossifying fibromas and myositis ossificans	Giant-cell tumor
B Tumors of Nonosseous Origin		
Marrow and Haversian Systems	*Metastatic Deposits*	*By Inclusion or Direct Invasion*
Ewing's endothelial myeloma	Carcinoma of prostate, breast, kidneys, etc	Chordoma
Multiple myeloma	Metastatic lymphomas, neuroblastoma and sarcomas	Angioma, angiosarcoma
Chloroma and leukemia of bone		Lipoma, liposarcoma
Reticulo-endotheliosis		Fibroma and fibrosarcoma, fascial or nerve sheath
Xanthomas and granulomas of bone		Myosarcoma synoviomas

developmental patterns rather than to embryogenic abnormalities, such as was postulated by the Cohnheim theory For this reason a review of the embryology of bone is pertinent to any study of skeletal tumors.

The bony skeleton of man represents the highest degree of differentiation in the supporting tissues of the body In its adult form it consists of bone, of cartilaginous articular surfaces fluid-containing synovial compartments (joints) and ligamentous and tendinous attachments to bind the whole together and to furnish attachments for the overlying musculature. All these skeletal structures are derived from a primitive skeletogenic tissue which is a derivative of the somatic mesenchyme. The various types of specialization seen in the adult state represent differences in the nature of the cement substances elaborated by the skeletogenic cells, rather than a fundamental difference in the cytologic elements. These cement substances, collagen, hyalin and bone, are to be looked upon as derivatives of the cell wall and the intercellular substance rather than integral parts of the cyptoplasm. It is only with full realization of the extracellular nature of the specialized cement substances that the interchangeability of fibrous tissue, cartilage and bone at varying stages of *development can be appreciated. Thus, in* the scorbutic animal, bone can regress to fibrous tissue, and cartilage to precartilaginous connective tissue. This is a reversal of the processes of ossification and chondrification seen in the normal animal. Moreover during normal development a resorptive tissue characterized by vascularization and giant cells attacks preformed cartilage that is to be replaced by cancellous bone. The same tissue attacks cancellous bone when it is to be converted into compact bone.

EMBRYONIC PROCESSES CONCERNED IN THE FORMATION OF BONE TUMORS

In the lowest form of vertebrate animals connective tissue differentiated from primitive mesenchyme and distended by a coagulable fluid forms the notochord, the only skeletal element. Later in evolution, cartilage and then bone both differentiating from the primitive mesenchyme, take part in the formation of the skeleton. This sequence is repeated in human embryology (Fig 11) All components of bone, whether fibrous cartilaginous or osseous, are derived from a preformed connective tissue. This mesenchymal tissue, which condenses in the embryo at the site of the future skeleton (known as the skeletal blastema or skeletogenic mesenchyme) may either develop into cartilage as in the endocartilagenous skeleton or may develop directly into membranous bones, as in the face and cranium (Fig 6)

Where the membranous bones of the skull arise direct intramembranous ossification occurs in the connective tissue at one or more central points. The spindle cells of the connective tissue are transformed into osteoblasts which lay down spicules of bone. Osteomas composed of varying amounts of fibrous tissue and bone are common tumors arising in connection with this form of ossification in the skull. In the long bones of the axial skeleton, direct ossification in fibrous tissue may form osteoid tumors (osteoid osteomas and fibrous dysplasia) Growths *corresponding to cranial osteomas in the* extremities are usually extraskeletal and form in bursae or in the muscles (myositis ossificans)

In most of the skeleton, where cartilage precedes bone, the connective tissue transforms into small, rounded fetal cartilage cells. They later give rise to adult hyaline cartilage which gradually calcifies. In the formation of bone this cartilage after calcifying, undergoes destruction Ossification occurs within the eroded cartilage and, peripherally beneath the perichondrium by the formation of osteoblasts. Peripherally the osteoblasts are derived from periosteum. Centrally cancellous bone (replacing cartilage) is derived from the endosteum. This endosteum penetrated the eroded cartilage along with an ingrowth of blood vessels and

lays down spongy bone (Fig. 7) In the process of bone formation the osteogenic tissue is formed from the inner layer of the perichondrium (the periosteum) and within the medullary canal (endosteum) and thenceforth the process of ossification is final process of ossification. The process is reversible and in many pathologic processes the compact osseous tissue is resorbed, to be replaced by a looser cancellous structure. This is true of deficiency states such as osteomalacia and Paget s osteitis deformans



Fig. 6 Human embryo—140 mm. (A) shows the condensation of embryonic connective tissue (blastema) at the site of the future skeleton. In (B) this precartilaginous condensation of connective tissue is giving rise at its center to early cartilage cells. *The persisting rim of dense connective tissue about* the early cartilage cells is the primitive perichondrium and has the power of forming both bone and cartilage. Persisting strands identical in nature with the perichondrium are referred to as precartilaginous connective tissue

identical with that in the membranous bones.

Although differentiated cancellous and compact bone in the skeleton are the result of the activity of fibroblasts which transform into osteoblasts and thence into osteocytes, this ossifying tissue is unable to perform its highest function of laying down differentiated bone unaided. In order to form bone, which utilizes a complex salt of calcium carbonate and phosphate, an adjacent store of the mineral must be available For this reason compact bone requires either the pre-existence of calcified cartilage or spongy cancellous bone These are vascularized and resorbed during the and in the atrophy of bone following disuse A certain amount of this process takes place during pregnancy and whenever the available mineral stores are depleted, as in hyperparathyroidism, rickets, hypo- or hyper thyroidism and in celiac disease or steatorrhea.

The final products of ossification thus feed on a pre-existing source of mineral material and, in turn, constitute a source of such minerals whenever the need in the body arises. This lability of osseous structures is usually characterized during its active phase by a highly vascular conn tive tissue in which giant-cell osteoclas prominent. This resorptive phase

herein termed *Angiospongiosa*, is an essential developmental process and is a frequent source of tumor formation (bone cysts and benign giant-cell tumors) This vascular process is also conspicuous in osteolytic forms of osteogenic sarcoma

are found periosteally periarticularly or near the anchoring of muscular tendons at bony tuberosities, are responsible for such growths (Müller Köllicker Ewing)

Strands of primitive precartilaginous tissue, which in the embryo form the joint



FIG. 7 Human embryo--90 mm. Cross section of the future humerus, showing calcified cartilage surrounded by a cuff of osteoid tissue This osteoid tissue has been formed by the cellular periosteum shown in the lower right hand corner In the center of the picture is a giant-cell osteoclast which has perforated the osteoid cortex and is about to carry out the function of cartilaginous resorption to form the marrow cavity within the bone.

The majority of tumors of osseous origin affect the bones which are preformed in cartilage. Persisting islands of cartilage in an arrested state may be found within the medullary substance of the long or flat bones in adults (Fig 11H) These remain quiescent or undergo subsequent growths, giving rise to central chondromas. More frequently however persisting strands of precartilaginous connective tissue, which

cavities by mucoid regression, normally remain after birth at the margins of skeletal articulations. They may show active growth at the reflexion of the joint capsule or at points of attachment for tendons and ligaments (Fig 8) Such tissue is responsible for joint tumors known as chondromatosis of the joint and for the periarticular osteophytes found in arthritis. These precartilaginous strands may also be found some

distance from the joint, where, by their power of cartilage and bone formation, they aid in the building of normal bony protuberances for the insertion of the important tendons. At such points, these developmental processes may give rise to benign exostoses (osteochondromas) or to osteogenic sarcoma containing cartilage (chondromyxosarcoma) In the small bones of the hands and feet or about the vertebrae and ribs, where this early blastemal tissue has been unusually active in joint formation, aberrant strands may give rise later in life to benign central chondromas. Osteogenic sarcoma, of a strictly osteoblastic type, may also arise from this primitive connective tissue beneath the periosteum in the metaphyseal region of the long bones. The periosteal osteogenic sarcomas, which arise in this way are related to the osteoblastic functions of the newly formed periosteum, which is converted perichondrium. Osteoblastic sarcoma also may arise from endosteum.



FIG. 8. Human embryo—140 mm. Low magnification of the bones about the knee joint. The bones have been preformed in cartilage. About this cartilage the dense embryonic connective tissue, which is the forerunner of cartilage, persists. Note that this early connective tissue is present in the future joint cavity and also adheres at the places where the tendons are forming

From the standpoint of tumor formation, there are several important features concerning the embryology of precartilaginous connective tissue under discussion First, the skeletal blastema persists as such normally in adult life within the skeleton in the region of the periosteum and the perichondrium of the joint surfaces. It also persists as such in extraskeletal locations, within the joint cavity, in the synovial membrane, and periarticularly (at the reflexion of the joint capsule) and at the attachment of important tendons and ligaments to the bone. It can be readily identified histologically through its composition of compact, small spindle cells. When undergoing tumor formation it is characterized by two additional features (1) its tendency to form both cartilage and bone in adjacent islands, and (2) the sparsity of a resorptive phase (in which blood vessels and osteoclasts predominate) in the tumor growth. There are additional clinical features concerning tumors derived from precartilaginous connective tissue. First, those of periosteal origin may be either benign or malignant. The benign growths, such as osteochondroma, have a special predilection for the sites of insertion of certain tendons. These are at the insertion of the adductor magnus muscle above the medial condyle of the femur of the quadriceps tendon, on the medial aspect of the upper tibia in the deltoid tuberosity on the upper lateral aspect of the humerus and in the region of the femoral trochanters. These are locations in which extraskeletal blastema persists to aid in anchoring the tendons of important muscles, and these growths may be considered as exaggerations of normal bony protuberances for the anchoring of important muscles. When undergoing tumor formation, these foci of extraskeletal blastemas show their normal developmental transitions. The tissue cycle passes from condensed mesenchyme to fetal cartilage to adult cartilage overlaid by strands of ossifying connective tissue. The neoplastic proc

ess, therefore, accelerates the rate of growth of such tissue but fails to distort its pattern of differentiation It is significant therefore, that osteochondromas occur usually in adolescence, when skeletal growth is under maximum physiologic stimulus. A single tuberosity may be picked out for tumor formation during the period of maximum stimulation, suggesting that the extraskeletal tissue is abnormally sensitive to tension during the period of maximum bone growth. The maximum age incidence is during adolescence between the periods of 10 and 20 years.



FIG 9 Monkey fetus at term. Longitudinal section of a femur of a monkey fetus showing the shaft of the bone completely ossified and the persistence of cartilage in small amounts in the metaphyseal region The epiphyses are still composed entirely of cartilage

The primary chondromyxosarcomas are rapidly growing malignant tumors which show the same transitional steps in development (connective tissue cartilage and bone) as the osteochondromas. Whereas, in benign osteochondromas, adult cartilage and bone predominate in the sarcomatous lesions fetal cartilage cellular connective tissue and islands of calcification predominate. Bone formation is relatively sparse. Moreover the intermingling of the various transitional areas is less orderly in the tumor as a whole. In other words, anaplastic rather than differentiated tissue predominates. The age incidence and the sites for these new growths, however are similar to those of the benign lesion The conclusion is that the tissue of origin for both growths is the same. The factors precipitating the neoplasia must be quite different in order to account for the markedly contrasting growth rate which distinguishes the malignant from the benign lesions.

Sclerosing osteogenic sarcoma is similar in its age and skeletal distribution to chondrosarcoma except for the greater tendency of the tumor to occur on the medial aspect of the lower femur and the medial aspect of the upper tibia, on either side just behind the epiphyseal line, in a subperiosteal location The periochondrium involved has already passed through its precartilaginous stage during the process of normal development and is in the preosseous stage. As a result, in the tumor formation cartilage is either absent or formed in only minimal amounts.

SUMMARY OF EMBRYOGENESIS

In the endochondral bones, cartilage is the first specialized mesenchymal derivative to make its appearance As the fetal cartilage cells develop the rim of the mesenchymal condensation remains behind to develop as primitive perichondrium or periosteum, a form of preskeletal connective tissue (Fig 6) As long as the bone grows, from early fetal life to the age of 20 years or more cartilage persists at the growing end in the form of epiphyseal plates. Apparently this gelatinous, hyaline cement substance, which forms a warehouse for the

storage of calcium and phosphorus ions is essential to rapid and orderly bone construction outside of the membranous bones. Lacroix has cited evidence to indicate that this cartilaginous plate acts as organizer for the adjacent ossifying connective tissue.

At about the middle of fetal life, when the long and flat bones of the body have been preformed by cartilage, they receive a periosteal blood supply from the surrounding tissue. At the point of a maximum vascularity in the midshaft region, a periosteal cuff of bone is formed. Shortly thereafter this periosteal blood supply in the midshaft region penetrates the cuff of periosteal bone and the underlying cartilage (Fig 7) From there onward, ossification proceeds in two directions (1) at right angles to the cartilaginous shaft in the form of periosteal bone and (2) along the central axis parallel to the shaft, towards the ends of the bone. The circumferential bone is known as periosteal bone. The longitudinal bone is known as endosteal bone (Fig 10) The periosteal bone is vascularized and reformed at intervals to form compact bone The endosteal bone is vascularized to provide space for the bone marrow and is replaced by coarse trabeculae of cancellous bone. Both the periosteal and the endosteal types of bone-growth progress away from the midshaft region toward the ends of the bone, so that at puberty both periosteal and endosteal bone are at their maximum just behind the epiphyseal cartilaginous plate.



FIG. 10 Monkey fetus at term Section taken from the specimen shown in Figure 9 emphasizing the role of giant-cell osteoclasts in the resorption of calcified cartilage. This resorption of calcified cartilage by giant cells precedes the formation of permanent cancellous bone and the creation of the marrow cavity

Since at puberty these processes are at their maximum degree of intensity they are then most sensitive to abnormal influences. Most benign and malignant tumors of bone occur therefore, during adolescence and in the triangle just behind the cartilaginous plates, where the following processes occur in rotation

1 Cartilaginous growth.

2. Resorption and vascularization of calcified cartilage.

3. Endosteal and periosteal ossification from fibrous tissue.

4. Revascularization and reformation of endosteal and periosteal bone to produce cancellous and compact cortical bone.

In bone tumors related to osteogenesis, all these phases of skeletal growth are represented.

1. Cartilaginous growth is represented by the chondromas, the chondromyxomas and the chondrosarcomas. A more primitive cartilaginous phase is represented by chondromas.

2. Vascularization of calicified cartilage of preformed bone, with resorption by vessels and giant cells, is represented by giant cell tumors and by osteolytic osteogenic sarcomas.

3. Ossification in fibrous tissue is represented by osteomas, ossifying fibromas, osteoid osteoma, fibrous dysplasia myositis ossificans and by sclerosing osteogenic sarcomas.

4. Combinations of the foregoing also occur Osteochondromas are a combination of cartilaginous growth and ossifying fibrous tissue. Chondroblastomas are a combination of cartilaginous growth, combined with vascular resorption and giant cells. Bone cysts are combinations of vascular resorption, overlaid by healing resection with ossifying fibrous tissue.

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PART TWO

Tumors of Osseous Origin

2

Osteochondromas

Approximately one half of all primary neoplasms of the bone are related to pre cartilaginous connective tissue. The tumors in this group include the osteochondromas, the chondromas, the chondromyxosarcomas, and in addition, some osteoblastic sarcomas of a more highly differentiated bone-forming type. Taken broadly the first three of these lesions represent different stages of the same pathologic process and may be graded from the more primitive and malignant to the more highly differentiated and benign—the most primitive, the chondromyxosarcomas, being malignant, the chondromas being potentially malignant in their recurrent form and the osteochondromas being essentially benign. Histologically also, there is no sharp dividing line between these three forms of neoplasms since the basic tissues comprising them, connective tissue, cartilage and bone, are present in varying amounts in all these growths.

This combination, or rather transition, from connective tissue to cartilage and to bone seen in all these tumors, repeats not only the sequence by which portions of the skeleton are derived in the embryo, but recalls the order of development of the spine in vertebrates and demonstrates effectively the relationship of tumors of the bone to both evolution and embryology (Fig 11) For in its primitive form the vertebrate spine or notochord is membranous, composed of cellular connective tissue distended with fluid (myxomatous) Later the notochord gives way to cartilage, to be replaced in the higher forms by a vertebral column composed almost entirely of bone.

The osteochondromas, or exostoses, are benign tumors, usually occurring in persons between the ages of 10 and 25 years. They are situated near the end of the long bones and form bony skeletal outgrowths with a thin cartilaginous cap. The symptoms are generally mild and of long duration, averaging over five years. The roentgenogram of the involved bone has characteristic features. These are an osseous base or pedicle, springing directly from the cortex of the underlying bone without an intervening zone of abnormal osseous tissue and an overlying expanding cap composed of cartilage undergoing calcification. Microscopic examination of the excised tumor reveals normal laminated bone beneath a transitional zone of lobulated cartilage which is overlayed by a thin strand of fibrous tissue. Histogenetically it will be shown, these tumors are an exaggeration of normal bony protuberance intended for the anchoring of an important tendon.

CLINICAL FEATURES

While the roentgenogram and the microscopic section of an osteochondroma usually present fairly uniform changes, many of the clinical features of this lesion are notably variable. This type of skeletal outgrowth, which is generally continuous with the bone but may rarely be entirely separated from it and embedded in the substance of a tendon or of a soft part struc-

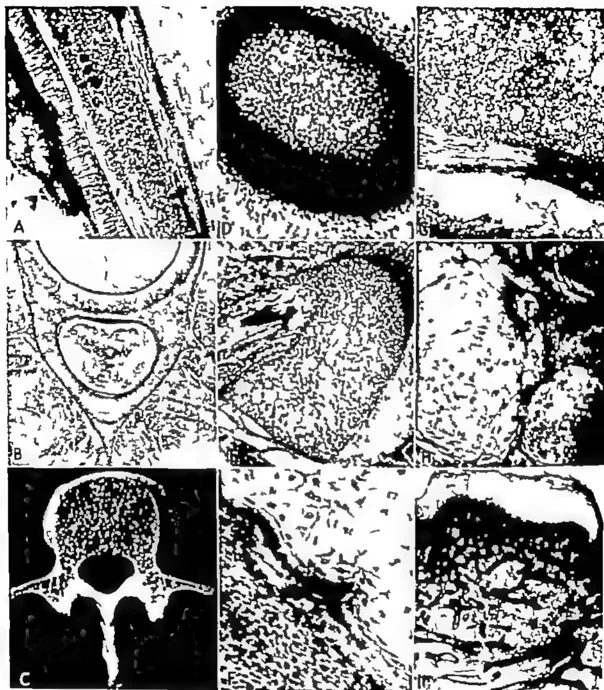


FIG. 11 Comparison of the cycle of development in skeletal tissues in evolution (A, B C) in the embryo (D E, F) and in tumors related to precartilaginous connective tissue (G H, I) (A) A longitudinal section of the membranous spine or notochord of the amphioxus, one of the most primitive of the vertebrates, (B) the essentially cartilaginous structure of the vertebrae in the dogfish, an animal well along in the scale of evolution of the vertebrates; (C) the osseous structure of the adult vertebrae in man, (D) the first step in the formation of the skeleton in the human embryo, with primitive connective tissue or mesenchyme condensing at the site of the future skeleton, (E) the early formation of cartilage from primitive connective tissue in the human embryo; (F) a rim of permanent bone being laid down about calcified cartilage which is being resorbed by giant cells, one of which is shown in the picture. This is the first stage of ossification in the human embryo. (G) shows the microscopic appearance of a chondromyxosarcoma at the margin of the tumor The neoplastic

ture, is associated with many different etiologic factors. Some of these tumors are undoubtedly congenital in addition, there is often a distinct familial history Cases in which several members of the same family in one or more generations are affected by multiple outgrowths of the exostosis type are by no means rare (Ehrenfried) The development of osteophytes identical in histologic structure with such congenital exostoses may take place in adult life as the result of chronic infection, the calcaneal spurs in chronic gonorrheal arthritis being a common example

While osteochondromas are essentially a neoplasm of the early decades with the peak of the curve of age incidence between 10 and 20 years, about 30 per cent are observed in patients over 30 years of age (Chart 2) Those exostoses in patients under 30 are usually truly neoplastic and rarely infectious. These same types of exostoses occurring early in life also may be recorded in patients well over 30 since the absence of symptoms often permits a latent period of more than 25 to 40 years. This tendency of osteochondromas to remain latent or evade clinical observation is shown by the fact that although more than 25 per cent of these lesions apparently date from birth, only 6 per cent are observed clinically in patients less than 10 years of age

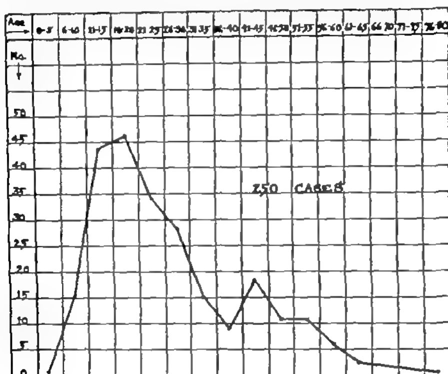


CHART 2. Chart showing the age incidence of benign osteochondromas, or exostoses.

Figure 12 shows the skeletal distribution of these exostoses. In analyzing the distribution of these tumors, it was found that nearly twice as many males were affected

Ehrenfried, A. Hereditary deforming chondrodysplasia, multiple cartilaginous exostoses a review of the American literature and report of twelve cases, J. A. M. A., 68 502, 1917

tissue is a proliferation of embryonic connective tissue and fetal cartilage cells or so-called myxoma. (H) shows the essentially cartilaginous structure of a benign chondroma, and (I) the predominantly osseous structure of a benign osteochondroma

TABLE 2. BENIGN OSTEOCHONDROMAS (EXOSTOSES)

Pathologic No	Race	Sex	Age	Location	Duration	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
62918	W	F	6	Lower right femur	Not stated	Tumor	Pedicle exostoses with cartilaginous cap	Excision, 1943	Osseous base chondral cap	
62272	W	F	19	Lesser trochanter	14 mos.	Soreness and pressure, femoral vessels	Trabeculated cancellous bone with intact thin cortical shell	Excision 3-18-43		Well 5 yr
62312	W	M	10	Left tibia	8 mos.	Some pain	Not stated	Excision 10-10-42	Osseous base chondral cap	
622[illegible]0	W	M	28	Lower right femur	24 mos.	Tumor	Typical exostosis	Excision	Osseous base chondral cap	
62228	W	F	13	Left humerous	Not stated	No pain or tenderness	Benign recurrent exostosis	Excision 7-0-42	Typical benign exostosis	
62220	W	M	10	Upper left tibia	12 mos.	Tumor	Not stated	Excision	Osseous base chondral cap	
62196	W	M	0	Right arm	5 wks.	Pain	Ossifying periosteal reaction			Lost
62080	W	F	50	Distal end metacarpal bone, left index finger	5 mos.	Swelling and slight pain	Osseous tissue and calcareous stippling			Well 7 yr
61314	W	M	7	Upper right humerus	10 mos. following injury	Tumor	Typical osteochondroma			
61310*	W	M	18 mo	Lower femora	6 mos.	Bowed legs	Congenital dystrophy involving cartilaginous centers in bones of lower extremities			
61188	W	M	11	Right elbow	2 mos.	Trauma	Mushroom-shaped osseous tumor			Well 8 yr
61120	W	M	12	Shoulder	6 wks.	Discomfort	Typical exostosis	Excision	Osseous base chondral cap	

61054	W	F	18	Right knee	6 wks.	Pain and swelling	Pedicle exostosis cartilaginous cap			
61018	W	M	23	Left great toe	7 mos.	Pain				Well 0 yr
60838	W	M	5	Pubic area, left	6 mos	Tumor	Rarefaction and bony protuberance at site of junction of left pubic and ischial bones			
60082	W	F	9	Bottom of foot	6 mos.	Subsequent pathologic fracture	Not stated	Excision 1939	Osseous base chondral cap	
60038	W	M	20	Lamina of lumbar vertebra	2 yr	Compression of spinal cord	Not stated	Excision 1943	Osseous base chondral cap	
59752	W	M	12	Lower third tibia	1 yr	Pressure on fibula causing lateral bowing	Benign exostosis, 6-7-38 recurrent, 10-1-38	Excision June, 1938 Excision 10-8-38	Recurrent osteochondroma	Lost
59238*		M	16	Multiple chondromas (chondrodysplasia)	2 yr	Swelling in region of joints	Pathology is found in all areas where cartilaginous features have previously existed or exist at present	None		
59158	W	M	16	Tibia, right	4 mos	Symmetrical enlargement	Typical benign osteochondroma upper third tibia	Excision 6-27-38	Osseous base chondral cap	Well 10 yr
58970	W	M	39	Interphalangeal joint, middle finger right hand	5 yr	Tumor	Osteocartilaginous tumor exostosis	None		Lost
58110	W	M	12	Medial aspect distal portion of femur	8 mos.	Swelling	9-21-33 diagnosed osteophyte 9-22-36 diagnosed osteochondroma			Well 15 yr

TABLE II. BENIGN OSTEOCHONDROMAS (EXOSTOSES) (*Continued*)

Pathologic No	Race	Sex	Age	Location	Duration	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
57778	W	F	[illegible]	Right upper jaw bicuspid region	10 yr	Tumor	No periosteal reaction no bone destruction appears benign 1-4-37	Biopsy for diagnosis 1-4-37	Osseous base chondral cap	
57538	W	F	24	*Upper femur*	4 yr	Slight pain	Typical benign osteochondroma			
57580	W	M	32	Pubic bone	2 yr	Tumor	Pedicle of normal bone proceeding from the pubis	Excision Oct., 1936	Osseous base chondral cap	
56870	W	M	9	Left os calcis	6 mos.	Tumor pain	Bony protuberance, posterior *surface*	Excision 7-8-36	Osseous base chondral cap	Osteopetrosis 7 yr later
56862	W	M	12	Right scapula lower border	2 yr	Swelling no pain	Calcareous stippling in cap of tumor			
56432	W	F	[illegible]	Greater trochanter and neck of femur	*2½ yr*	Pain	Calcified growth overlying neck of femur calcified shadows in soft parts			Well 4 yr
56392	W	F	23	Wing of left ilium	3 mos.	Swelling	Not stated	Excision March, 1936	Osseous base chondral cap	Well 4 yr
56376	W	M	11	Left tibia	Since early childhood	Tumor	Benign exostosis with inflammatory bursa	Excision 3-6-36	Osseous base chondral cap	
56336	W	M	12	Upper humerous below epiphyseal line	6 mos.	Tumor	Not stated	Excision Feb., 1936	Osseous base chondral cap	
56230	W	F	17	Inner astragalus	2 yr	Severe pain	Exostosis	Roentgen excision		
56120	W	M	12	Multiple exostoses and enchondromas	3 yr	Pain	Zones of encapsulating bone and calcification			

56042	W	M	10	Upper fourth left tibia	8 wks.	Pain	Not stated			Lost 1948 wearing brace
55172*	W	M	0	Multiple exostoses	2 mos.	Pain in ankle	Multiple benign exostoses			Increased deformity
55292	W	F	23	8th rib left	17 yr	Swelling	Osteochondroma	Excision 5-15-35	Osseous base chondral cap	
55131*	W	F	11	Multiple exostoses	2 yr	Pain	Multiple exostoses			Lost
51238	W	F	31	Lower femur	2 yr	Pain	Calcified cartilaginous cap surmounting a pedicle of cancellous bone	Excision 11-15-34	Osseous base chondral cap	Lost
53950	W	M	10	Right ischium	2 mos.	Trauma, pain	Cartilaginous lesion exostosis			Lost 1948
53048	W	M	15	Lower femur	7 mos.	Tumor	Typical benign exostosis			Lost 1948
53464	W	F	33	Femur lateral side	Not stated	Tumor fluid in knee joint, nodular area above joint	Cauliflowerlike growth exostosis	Roentgen 1931 Excision 1942		Well 14 yr
52416	W	M	19	Fibula, left	1 yr	Tumor		Surgery biopsy	Osseous base chondral cap	Well 3 yr
52020	W	M	10	Os calcis, left	2 yr	Swelling	Definite spur on os calcis near astragalus soft part shadow around tendon		Osseous base chondral cap	
52444	W	F	10	5th lumbar vertebra	4 yr	Pain	Cystic or cartilaginous change	Excision 12-5-33	Osseous base chondral cap	
51056	W	M	20	Os calcis	4 yr	Enlargement	Osteochondroma resting upon os calcis on medial aspect	Excision 1933	Osseous base chondral cap	Well 15 yr
51036	W	M	40	4th lumbar vertebra	1 mo	Pain	Clearly demarcated osseous and calcified lines benign osteochondroma	Excision 1-7-33	Osseous base chondral cap	Lost 1948

TABLE 2. BENIGN OSTEOCHONDROMAS (EXOSTOSES) (*Continued*)

Pathologic No	Race	Sex	Age	Location	Duration	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
50098	W	M	18	Right femur	3 mos.	Pain	Cartilaginous cap exostosis			Lost 1948
19882	W	M	14	Femur	3 mos.	Rapid increase in size	Pedicle type of exostosis with large califlower like calcified mass	Excision 1-3-33	Osseous base chondral cap	Well 5 yr
40402	W	M	27	Femur left	3 da.	None	Exostosis no bone erosion at base	Excision 1932	Osseous base chondral cap	Well 15 yr
40206	W	M	30	Phalanx left great toe	Pain 2 yr after fracture	Pain	Peculiar form of exostosis, benign	Resection 5-10-32 resection 10-13-32	Second section shows no malignant change	
48474*	W	F	38	Humerus	2 mos.	Pain	Benign exostosis, multiple			Unchanged 16 yr later
47362	W	M	32	Big toe	3 mos.	Tumor		Excision	Osseous base chondral cap	Well 7 yr
45616	W	M	10	Tibia	6 mos.	Tumor				Well 5 yr
45152	W	F	21	Ulna	1 yr	Tumor		Irradiated 1932		Well 7 yr
30180	W	M	[illegible]	Humerus	Few wks.	Tumor		Roentgen		Well 8 yr
30136	W	M	0	Humerus	3 mos.	Tumor		Roentgen		Well 11 yr
10545	W	M	43	Os calcis	4 yr	Tumor	Osteochondroma	Excision	Osseous base chondral cap	Dead 16 yr later heart disease
27702	W	F	18	Fibula	2 yr	Tumor		Resection	Osseous base chondral cap	Well 13 yr
36638	W	M	60	Femur			Exostosis			Dead 15 yr later other cause

as females and that whites predominated, only 16 colored patients being present in this series of 310 cases. Nearly one third of the tumors occurred about the knee joint in the lower end of the femur or upper end of the tibia. The majority of the remaining tumors were located at the ends of the long bones of the ankle, the shoulder the hip or the elbow The other sites of importance are the region of the jaw and skull and the small bones of the foot or hand. It must be borne in mind, however that tumors of the skull and jaws often grouped under exostoses are, properly speaking, osteomas, representing a different type of ossification in fibrous tissue, and that some of the tumors of the small bones of the hands and feet fall into the category of aberrant sesamoid bones. Eight per cent of the cases were of the multiple, hereditary variety

The striking feature of the skeletal distribution of osteochondromas is their periarticular location and their relation to sites of tendinous attachments. These tendons are generally those involved in regions of maximal traction, being at the ends of such muscles as the adductor magnus and quadriceps femoris in the thigh and the gastrocnemius and soleus at their convergence in the Achilles tendon. A further peculiarity of these sites is the fact that the tendons attach not to the periosteum but directly to the bone.

The average duration of symptoms for the cases of osteochondroma listed in Tables 2 and 3 is 61 months, or slightly over 5 years. This duration of symptoms corresponds closely to the average time of 4½ years computed by Meyerding in a study of 232 cases reported from the Mayo Clinic. This protracted course bespeaks benignity for in this condition, as in most neoplasms, the longer the duration of symptoms the greater the curability of the disease.

The benign course of these lesions is indicated also by the character of the symptomatology Pain is rarely severe, and when other than a mild ache or discomfort is present, there is usually some complicating factor Such complicating factors may take the form of bursitis or inflammation from irritation in the overlying soft parts, or repeated trauma may bring on such a condition in a region where swelling interferes with the use of the affected member

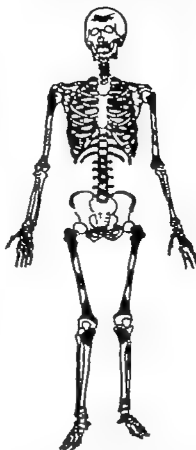


FIG. 12. Incidence of osteochondromas according to skeletal location. The solid black areas indicate the most frequent sites, the checked areas, the common sites; the diagonal lines, the occasional or rare locations.

More rarely acute symptoms may follow a sudden increase in the rate of growth in the tumor Compression of important vessels may cause edema and pain and bring the patient under observation. When such acute symptoms can be attributed to an increased growth rate in the tumor malignant change is always to be suspected. It is a

Meyerding, H. W Exostosis, Radiology 8 282, 1927

TABLE 3. BENIGN OSTEOCHONDROMAS (EXOSTOSES)

Pathologic N	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment‡
44619*	N	M	18	Tibia, left	4	Pain; tumor	Multiple pedicle exostoses	Excision, Jan. 31, 1929	New bone	Discharged well
44257	W	F	48	Femur external condyle	24	Fracture; pain		Excision, November 1928	Cancellous bone; old cartilage	Discharged well
43891	W	F	86	Toe				Removal of toe		Discharged well
43449	W	M	16	Tibial tuberosity	79	Trauma; pain; tumor	Bursa over exostosis with cartilaginous cap	Exploration	Cancellous bone; adult cartilage	Discharged well
4.497	W	M	14	Femur lower right	[illegible]	Trauma; pain; tumor		Excision, June, 1928	Cancellous bone; adult cartilage; some fetal cartilage	31 mos. well
43347	W	M	18	Toe, left	6	Tumor		Excision, May 1928	Cancellous bone; old cartilage	Discharged well
43184	W	M	40	Thumb, left	36	Tumor	Rounded exostosis	Excision, March, 1928	Cancellous bone; adult cartilage; some new bone	Discharged well
43095	N	F	22	J w lower	96	Tumor; deformity of mouth		Excision, March 1928	Cancellous bone; old cartilage	Discharged well
43042	W	M	20	Fibula	6	Pain; tumor	Broad exostosis; cartilaginous cap	Excision, June, 1930	Calcifying cartilage; osteoid tissue	Well 10 yr
42797	W	F	18	Skull, frontal	144	Trauma; tumor	Rounded exostosis	Excision, February 1928	Cancellous bone	Discharged well
42142	W	M	11	Tibia, upper left		Tumor	Cystic periosteal shadow			
41825	W	M	19	Foot, dorsum	48	Trauma; pain; tumor	Rounded exostosis over joint	Exploration, Aug 1 1927	Cancellous bone; adult cartilage	Discharged well
41563	W	M	18	Femur		Tumor		Excision, June 24 1927	Cancellous bone; adult cartilage	Discharged well
41519	W	F	18	Toe, right foot	2	Pain; tumor		Excision, June 18, 1927	Cancellous bone	Well 3 yr
41267	W	M	30	Femur and tibia		Tumor		Excision, M y 2, 1927	Cancellous bone, adult and calcified cartilage	Discharged well
41290	W	F	63	Foot, second metatarsal	3	Trauma; pain	Bone formation with transverse fracture	Biopsy	Cancellous bone	1 yr well
40896	W	M	13	Tibia, lower end	9	Trauma, pain; tumor	Rounded exostoses			
40703	W	F	9	Humerus, upper end	5	Tumor	Rounded exostosis, cystic	No operation		W ll 3 yr
40652	W	M	20	Fibula and tibia	96	Tumor	Rounded exostosis, cystic	No operation		
40648	W	7 M		Humerus, upper	9	Tumor	Cystic periosteal shadow	N operation		Well 4 y
40645†	W	M	15	Femora, multiple	180	Congenital tumors; abnormal gait		Excision, January 1927	Cancellous bone; calcified cartilage	Discharged improved
40623	W	M	20	Humerus	6	Tumor		Excision, J nuary 1927	Cancellous bone; adult cartilage	Discharged well

40343	W	F	32	Femur lower end		Tumor		Excision, March, 1929		1 mo. well
40280	W	M	40	Femur lower third	480	Traumat; tumor	Pedicle exostosis	Excision	Cancellous bone	2 yr well
40071	W	F	50	Toe, left foot		Tumor		Excision, October 1928	Cancellous bone; adult cartilage	Discharged well
40040	W	M	14	Femur interior left	24	Tumor	Pedicle exostosis	Excision, Jan 24 1928	Cancellous bone; adult cartilage	2 yr well
39933	W	M	43	Palat hard				Excision	Cancellous bone	Discharged well
39916	W	F	11	Humerus, upper third	24	Pain; tumor	Pedicle exostosis	No operation		14 yr well
39782	W	F	[illegible]	Radius, lower	60	Tumor	Pedicle exostosis	No operation		2 yr., condition unchanged
39502	W	F	12	Femur lower	1	Tumor	Broad exostosis; cartilaginous cap	Excision, July 1927	Cancellous bone; adult cartilage	13 yr well
39472	W	M	[illegible]	Femur lower	120	Tumor	Broad exostosis; cartilaginous cap	Excision	Cancellous bone; calcified cartilage	14 yr well
39445	W	M	41	Ilium, hip, right, acetabulum	36	Pain; tumor		Excision, June 9, 1926	Cancellous bone	Discharged well
39443	W	F	50	Femur, right, lateral condyle	6	Tumor		Excision, June, 1926	Cancellous bone; old cartilage	3½ yr well
39421	W	M	43	Maxilla, right	18	Tumor	Obliteration of antrum	Excision, June, 1926	Cancellous and new bone	Discharged well
39403	W	F	35	Maxilla, right	5	Pain	Obliteration of antrum	Excision, June, 1926	Cancellous and new bone	Discharged well
39173	W	F	18	Femur left				Excision, April, 1926	Cancellous bone; adult	Discharged well?
39064	W	F	30	Femur upper left	18	Pain; tumor	Cauliflower exostosis	None	New bone	Well 14 yr
38848	W	F	55	J w			Rounded exostosis	Excision, March, 1926		Discharged well
38784	W	F	107	Scapula, right	6	Tumor	Pedicle exostosis	Excision	Cancellous bone; adult cartilage	2½ yr. well
38780	W	M	45	Femur lower		Tumor	Pedicle exostosis			Well 2 yr
38694	W	F		Fibula, upper			Broad exostosis; cartilaginous cap			Well 3 yr
38613*	W	M	28	Femur right; fifth lumbar vertebra	96	Trauma; pain; tumor		Excision, 1926, 1928	Cancellous bone; adult cartilage	2 yr well
38466	W	M	28	Os calcis		Pain tumor	Pedicle exostosis in Achilles tendon	Excision, 1921		Well 6 yr
38400	W	M	12	Humerus, upper	½	Tumor	Broad exostosis; cartilaginous cap		Cancellous bone; calcified cartilage	Discharged well
38318	W	F	40	J w left, lower		Pain		Excision, November 1924	Cancellous bone; adult cartilage	Discharged well
37582	W	F	18	Humerus, shaft	4	Tumor; pain	Broad exostosis; cartilaginous cap	Excision, February 1929	Cancellous bone; adult cartilage	4 yr well
37549*	W	F	30	Humerus, left upper tibia, fibula, right	[illegible]	Tumor		Excision, 1925	Cancellous bone; adult cartilage	Discharged well
37373	W	M	[illegible]	Humerus, upper right	6	Trauma; tumor	Broad exostosis	Excision, May 1925	Cancellous bone; adult cartilage	
37365	W	F	21	Toe, right, little	12	Tumor		Excision, May 1925	Cancellous bone	Discharged well
37363	W	F	20	Tibia, lower	14	Pain	Broad exostosis; cartilaginous cap	Excision, November 1923		Discharged well

* Cases of multiple exostoses.
† Cases with typical hereditary deforming chondrodysplasia in which more than one member of the family was affected.
‡ The results of treatment shown have been figured from the date of the first operation.

Table 3. Benign Osteochondromas (Exostoses) (*Continued*)

Pathologic No.	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
37159*	W	M	21	Tibia, upper; upper right and left fibula			Multiple pedicle exostoses			Discharged well
36752	W	F	14	Fibula, left, upper	8	Pain	Broad exostosis; cartilaginous cap	Excision, manipulation, July 1925	Cancellous bone	5 yr well
[illegible]	N	M	43	Knee, left	6	Trauma; pain; tumor	Hypertrophic arthritis	Exploration		Lost
36642	W	M	13	Jaw lower left	3	Tumor; pain		Excision		5 yr well
[illegible]*	W	M	9	Tibia, shaft; femur upper and lower	13	Bow leg; slight trauma	Metaphyses widened and deformed	Straightening fracture		13 yr well
[illegible]			16	Arm		Trauma	Pedicle exostoses cartilaginous cap	Excision	Cancellous bone; old cartilage	Discharged well
35867	W	F	11	Humerus, right	48	Tumor		Excision	Cancellous bone; old cartilage	5½ yr well
35831	W	F	15	Toe, right, middle				Excision	Cancellous bone beneath normal nail-bed	6½ yr well
[illegible]	W	M	33	Tibia, internal condyle	60	Tumor; pain	Broad exostosis			
35760	W	M	30	Femur lower left	6	Trauma	Broad exostosis; cartilaginous cap	Excision	Fibrous tissue	Discharged well
35720	W	M	15	Tibia, upper	24	Trauma; tumor	Pedicle type with bursa	Excision	Cancellous bone, adult cartilage	Well over 1 yr
35716	W	F	15	Femur shaft	12	Tumor	Broad exostosis; cartilaginous cap			
35714	W	M	10	Femur shaft, lower third	48	Trauma; tumor	Pedicle exostosis; cartilaginous cap	Excision	Cancellous bone; adult cartilage; many giant cells	Discharged well
35713	W	F	16	Tibia, shaft, left internal condyle	42	Tumor	Broad exostosis, cartilaginous cap			5½ yr well
35661	W	M	24	Toe, large left; distal phalanx	168	Tumor		Excision, June, 1924	Cancellous bone; fetal adult and calcified cartilage	Discharged well
35634		M		Fibula, upper tibia, upper		Tumor; pain	Metaphyses widened and deformed			Lost
35333*	W	M	19	Tibia, upper and lower; fibula also	48	Tumors; multiple	Multiple pedicle exostoses, metaphyses widened			
35330		M		Femur left lower	36	Trauma	Broad exostoses; cartilaginous cap			5½ yr well
35366	W	F	18	Tibia, left, lower external	24	Tumor; pain	Broad exostosis; cartilaginous cap	Excision, June, 1924		5½ yr well
35227	W	M	21	Os calcis, right				Excision, April, 1924	Cancellous bone	Discharged well
35108		F	5	Temporal bone			Area of bone destruction under rounded exostosis			6 yr well

35070	W	M	23	Radius, upper right	6	Pain	Cystic tumor	Curettement, 1926	Cancellous bone; adult cartilage	6 yr well
34803	W	F	46	Os calcis, left	12	Tumor; pain		Excision, February 1926		6 yr well
34436	W	M	17	Femur shaft	9	Trauma	Flat, broad, ossifying periostitis			
34244	W	M	80	Auditory canal, external	10	Tumor		Not advised		
34167	W	M	39	Os calcis				Operation, October 1923	Cancellous bone; adult cartilage	Discharged well
33768	W	F	23	Skull, right	173	Tumor; pain	Rounded exostosis	N operation		Well 13 yr
33744	W	M	12	Tibia, left, upper	15	Tumor	Pedicle exostosis; cartilaginous cap	Excision, August, 1924	Cancellous bone	3½ yr well
33726	W	M		Humerus, external condyle		Tumor	Rounded exostosis	Excision, September 1923	Cancellous bone; adult cartilage	Discharged well
33750	W	F	15	Femur lower	24	Trauma; tumor	Broad exostosis; cartilaginous cap	No operation		
33533	W	M	19	Humerus, midshaft, right	229	Congenital tumor	Periosteal cauliflower mass	Excision, August, 1923	Adult cartilage; cancellous bone	Well 7 yr
33165	W	M	13	Humerus, upper right		Tumor fracture	Fracture through pedicle exostosis	Excision?		6½ yr well
33144	W	M	30	Femur lower right	24	Tumor; trauma; pain	Pedicle exostosis; cartilaginous cap	Excision, 1913, 1923	Calcified cartilage; adult cartilage; myxoma	Recurred; well, 1924
[illegible]	W	M	30	Pubis		Trauma; tumor	Rounded exostosis	Exploration, April, 1923	Adult cartilage	Well 7 yr
[illegible]	W	M	44	Scapula	19	Pain	Periosteal translucent area; rarefaction beneath			
3343	W	M	43	Pubis, left	4	Trauma, tumor	Broad exostosis; cartilaginous cap	N operation		Tumor larger 7 yr
32535	W	M	29	Femur lower right	36	Trauma; tumor; pain; limping	Rounded exostosis			Lost
32494	W	F	56	Ulna, styloid	73	Tumor	Sesamoid bone?	Operation refused		7 yr, well
32487	W	M	13	Skull		Tumor	Rounded exostosis	Excision, February 1923		Discharged well
32317	W	M	25	Femur shaft, right	19	Trauma; tumor; pain	Large periosteal calcifying mass	Exploration, January 1923	Adult cartilage; cancellous bone	Well 3 mos.
32267	W	M	43	Femur shaft		Pain; stiffness	Pedicle exostosis	No operation		7 yr well
32030	W	F	46	Femur lower	102	Trauma; tumor; pain	First, ossifying tumor; second, osteophytes in stump	Amputation, 1916; disarticulation, 1923	New bone; adult cartilage	Recurred; well, 1920
31932	W	M	6	Humerus, upper left		Tumor	Broad exostosis	Biopsy 1923	Hyaline cartilage and cancellous bone	Well 15 yr
31794	W	F	29	Humerus, upper	144	Trauma tumor	Large periosteal translucent area	Curetted, 1922; excised, 1924	Cancellous bone; adult cartilage	Well 11 yr
31532	W	F	[illegible]	Femur lower	30	Trauma; tumor	Pedicle exostosis; cartilaginous cap	Exploration	Cancellous bone	6 yr well
31133	W	M	17	Femur lower right	16	Tumor; pain	Pedicle exostosis			Well 8 yr after onset
31064	W	M	16	Femur lower, right	12	Tumor	Pedicle exostosis			
30890	W	M	30	Metatarsals, fourth and fifth, right	180	Trauma tumor; pain	Rounded exostosis	Excision, June, 1922	Cancellous bone	Discharged well

TABLE 3. BENIGN OSTEOCHONDROMAS (EXOSTOSES) (*Continued*)

Pathologic No.	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
30605*	W	F	29	Femur; tibia; fibula	102	Tumor; tenderness	Multiple pedicle exostoses	Excision	Cancellous bone; adult cartilage	Well over 7 yr
30453	W	M	19	Tibia, upper left		Pain	Pedicle exostosis	Excision		
30182	W	M	[illegible]	Femur lower right	[illegible]	Trauma; tumor	Pedicle exostoses			
30151	W	M	[illegible]	Femur lower right	60	Tumor	Broad exostoses			
30150	W	M	19	Femur lower right	12	Trauma; pain; stiffness	Pedicle exostosis			
30449	W	M	21	Femur lower right		Pain; tumor	Pedicle exostosis			
30136	W	M	30	Humerus, lower left		Tumor	Pedicle exostoses	Incised, March, 1923		7 yr well
30390*	W	M		Frontal bone, right; eth mole, right; maxilla, left		Syphilitic history	Multiple rounded exostoses	Antisyphilitic, 1922		Exostosis disappeared
30383	W	F	34	Occiput	12	Tumor	Broad exostosis			Unchanged 6 mo.
30304		M		Femur; trochanter; left	[illegible]	Pain		Excision, February 1922	Cancellous bone; adult cartilage	Discharged well
30265	W	M	18	Second metatarsal, right	½	Tumor		Excision, M y 1922		Discharged well
30186	W	M	40	Femur, upper		Tumor		Amputation, October 1917		Well 5 yr
30183	W	M	11	Humerus, upper left	½	Tumor	Rounded exostosis	Resection, June 1919		Well over 10 yr
30173	W	M	18	Lumbar first	24	Pain	Periosteal translucent area	Excision, September 1916	Cancellous bone; adult cartilage	W [illegible] 14½ yr
30129	W	F	50	Scapula	3	Pain; limitation of motion				8 yr well
30109	W	M	37	Humerus, greater tuberosity	36	Pain; limitation of motion	Broad exostosis	No operation		Condition unchanged
30045	W	M	16	Humerus, upper left		Tumor	Broad exostosis	Excision, March, 1922		Discharged well
29832	B	M		Humerus, lower left		Tumor		Excision, March, 1922		Discharged well
29747	[illegible]	M	21	Ulna, lower	144	Tumor; limitation of motion		Excision, April, 1921		Discharged well
29664	W	M		Femur neck, left	36	Trauma; pain; limitation of motion	Broad fuzzy exostosis	Excision, 1921; 1923	Cancellous bone; adult cartilage	Recurred, well 9 yr
29636	[illegible]	M	30	Femur neck	36	Trauma; pain; stiffness				Lost
20415	W	F	[illegible]	Index finger, right terminal phalanx		Trauma; pain	Rounded exostosis	Excision, January 1922		14 [illegible] well
29164*	W	F	30	Tibia; fibula; humerus		Tumors	Multiple pedicle exostoses	No operation		Unchanged 6 [illegible]
29009	W		16	Femur upper	36	Trauma; tumor	Broad exostosis			
29903	W	M	33	Femur lower right	43	Trauma; pain; adductor spasm	Broad fuzzy exostosis	Excision, September 1921	Cancellous bone; adult cartilage	Well almost 9 yr
[illegible]	W	F	12	Tibia, upper	36	Trauma; tumor	Broad exostosis; cartilaginous cap	Excision, September 1921	Cancellous bone; adult cartilage	Well almost 8 y

28701	W	M	11	Tibia, lower right		Tumor	Broad exostosis; cartilaginous cap	Excision, September 1921	Cancellous bone; adult and fetal cartilage myxoma in tendon	Well 9 mos.
29063	N	M	18	Femur		Tumor		Excision, August, 1921		Discharged well
29001	W	M	36	Femur shaft	312	Trauma; tumor	Pedicle exostosis	No operation		Condition unchanged
28996	N	M	10	Humerus, right		Tumor	Multiple broad exostoses	Excision, July 1921		Discharged well
28390†	W	M	9	Femur lower and upper; fibula		Tumors		No operation		Unchanged 9 yr
28223	W	F	30	Skull, frontal	225	Trauma; tumor; pain; strabismus	Rounded exostosis	Excision, May 1921	Cancellous and new bone	Well 1 yr
28083	W	M	11	Humerus, upper	36	Tumor	Broad exostosis; cartilaginous cap	Excision, 1921	Cancellous bone	Well 3 yr
27932	W	F	11	Clavicle	12	Trauma; tumor	Rounded exostosis	Resection, May 1910		Well almost 20 yr
27816	W	M	23	Humerus, upper right	24	Tumor; pain	Rounded exostosis	No operation		Condition unchanged
27697	W	M	29	Femur lower	240	Trauma; tumor	Pedicle exostosis	No operation		Condition unchanged
27308	W	M	18	Humerus, shaft	42	Trauma, tumor; pain		Excision, 1920		Well 8 yr
27225	W	M		Phalanx, second		Tumor	Rounded exostosis	No operation		Condition unchanged
27218	N	M	23	Os calcis		Gonorrheal arthritis	Calcaneal spurs	Excision, 1920	Cancellous bone; adult cartilage	Discharged well
27184	W	M	10	Femur left		Tumor		Excision, December 1920	Cancellous bone; adult cartilage	Discharged well
27147	W	M	11	Fibula, head		Tumor		Excision, November 1920	Cancellous bone adult cartilage	1 yr well
27079	W	F	19	Ilium	6	Tumor; pain	Fuzzy broad exostosis	Excision, April, 1910	New bone	20 yr well
27061	N	F	17	Tibia tuberosity	36	Trauma; pain	Broad exostosis	Excision, November 1920	Cancellous bone	Discharged well
26784	W	M	11	Radius, lower; humerus, upper	132	Tumors	Multiple pedicle exostoses	No operation		Condition unchanged
26738	W	M	25	Skull, frontal	270	Trauma; tumor; pain	Rounded exostosis	Excision, 1912; 1914; 1920	Cancellous bone	Repeated recurrences
26636	W	M	21	Navicular right wrist	4	Trauma; tumor; pain		Excision, August, 1920	Cancellous bone; adult and calcifying cartilage	9½ yr well
26410†	W	F	10	Multiple		Tumors	Multiple pedicle exostoses	Biopsy		Condition unchanged
26383	W	M	19	Mastoid	36	Tumor; pain; deafness		Excision, August, 1920	Cancellous bone; cellular fibrous tissue	Well almost 10 yr
26122	W	M	23	Skull, frontal	84	Trauma, tumor		Excision, July 1920	New bone; fibrous tissue	Well 1 yr
26093	W	F	14	Fibula, upper right	36	Tumor; pain		Excision, July 1920	Cancellous bone fetal and adult cartilage myxoma	Discharged well
26054	W	M	19	Femur lower	48	Tumor	Pedicle exostosis	Excision, 1910; 1920	Cancellous and new bone	Recurrence in 10 yr after second operation

TABLE 3. BENIGN OSTEOCHONDROMAS (EXOSTOSES) (*Continued*)

Pathologic No	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
25272	W	F	55	Humerus, right	36	Trauma; pain stiffness		Excision, June, 1920	Cancellous bone	Well 9½ yr
26120	W	F	60	Femur upper right	300	Infection		Excision, May 1920	Cancellous bone	
26097	W	M	51	Femur upper right		Tumor		Excision, 1920	Cancellous bone and adult cartilage	Discharged well
26036	W	F	47	Astragalus, right		Tumor		Excision	Cancellous bone and adult cartilage	Walking almost impossible after 10 yr
25835	W	M	10	Os calcis	14	Pain	Rounded exostosis	Excision	Cancellous bone and adult cartilage	Discharged well
25852	W	M	49	Radius, head		Tumor		Excision, March, 1920	Cancellous bone and adult cartilage	Discharged well
25603	W	M	11	Third lumbar vertebra, transverse process	37	Pain tumor stiffness		Excision, March, 1920	Cancellous and new bone	Discharged well
24422*	W	F	13	Humeri fingers tibiae	132	Multiple tumors	Multiple pedicle and broad exostoses	No operation		Condition unchanged
25123	W	M	47	Fifth lumbar vertebra	12	Pain on standing		Excision, October 1919	Cancellous bone	Well 10 yr
24988	W	M	19	Tibia tuberosity	24	Tumor				
24433	W	M	13	Tibia, upper	24	Tumor pain	Expanded, rarefied, subcortical area	Excision, April, 1919	Adult and calcifying cartilage	Discharged well
24212	W	F	19	Navicular left foot	33	Fracture tumor; pain	Fracture through exostosis			
24014	W	M	32	Os calcis	48	Gonorrheal arthritis; pain	Calcaneal spurs	Excision, January 1919	Cancellous bone in tendon	Discharged well
24003	W	F	24	Spine	48	Pain	Overgrowth in Albee transplant	Excision, May 1922	Cancellous bone in tendon	Discharged well
23860	W	M	30	Phalanx, little finger		Tumor	Pedicle exostosis	Excision, 1918	Cancellous bone; adult cartilage	Well 1 yr
23685	W	M	21	Tibia, upper	72	Tumor	Broad exostosis	Excision, December 1918	Cancellous bone; adult cartilage	Well 8 yr
23767	W	M	43	Femur neck	24	Pain; limitation of motion; gonorrheal history	Broad exostosis	Excision, November 1918	Cancellous bone; calcified cartilage	Discharged well
23500	W	F	37	Spine	12	Paraplegia		Excision, 1918; 1923	New bone	Died, 1926; decubitus ulcers
23563	W	M	16	Humerus, lower	14	Fracture; tumor; limitation of motion	Exuberant callus	Excision, August, 1918	Cancellous bone	Discharged well
23136	W	M	38	Big toe, right	60	Trauma; tumor	Broad exostosis	Excision, July 1918		
21966	W	F	10?	Humerus		Tumor		Excision, July 1918		Lost
22907	W	F	43	Femur left head	6	Pain; limitation of motion		Excision, March, 1918	Cancellous bone in tendon	Well almost 21 yr
22837	W	M	23	Os calcis, left	3	Gonorrheal arthritis	Calcaneal spur	Excision, February 1917	Cancellous bone; calcifying cartilage in tendon	Discharged well
22733	W	M	19	Os calcis		Pain	Calcaneal spur	Excision, January 1918	Calcified cartilage in tendon, synovium	13 yr well

22306	W	M	7	Humerus, shaft	60	Tumor; pain; limitation of motion		Excision, October 1917	Cancellous bone adult and underlying cartilage	Well 4 yr
22070	W	M	25	Femur lower left	240	Tumor	Multiple rounded exostoses	No operation		Well 11 yr
22003	W	M	25	Os calcis		Gonorrheal arthritis	Calcaneal spurs	Excision, August, 1917	Cancellous bone and calcified bone in tendon	Discharged well
21915	W	M		Humerus		Tumor		Excision, July 1917	Cancellous bone adult cartilage	Well over 12 yr
21680	W	M	34	Os calcis	60	Gonorrheal arthritis	Calcaneal spurs	Excision, June, 1917	Cancellous bone and cartilage in tendon	Recurred, arthritis
21492	W	M		Femur upper		Fracture; exuberant callus		Excision, February 1917	Cancellous bone adult cartilage	Discharged well
21424	W	M		Fifth lumbar vertebra		Pain; tumor		Excision, April, 1917	Cancellous bone; adult cartilage	Discharged well
21208	W	F	15	Femur lower left	24	Tumor	Pedicle exostosis	Excision, March, 1917	Cancellous bone; adult cartilage, myxoma	Well 13 yr
20881	W	M		Os calcis		Tumor; pain	Calcaneal spurs	Excision, January 1917	Cancellous bone	Well 2 yr
20787	W	M		Os calcis		Pain	Calcaneal spurs	Excision, January 1917	Cancellous bone; adult cartilage	Dead other causes
20303	W	M		Os calcis		Pain	Calcaneal spurs	Excision, October 1916	Cancellous bone; adult cartilage	Discharged well
20182‡*	W	F	6	Humerus, right; femur; left; ankle; wrist	60	Tumors	Multiple pedicle exostoses	No operation		Unchanged 6 yr
20156	W	M		Os calcis	4	Pain	Calcaneal spurs	Excision, September 1916	Cancellous bone; cartilage, myxoma	Well over 13 yr
18781	W	M	51	Vertebra, ninth dorsal	12	Pain		Excision, 1915 1916	Cancellous bone; adult cartilage	Dead, second operation
18607	W	M	26	Os calcis	48	Gonorrheal arthritis	Calcaneal spurs	Excision, December 1915	Cancellous bone	Arthritis recurred 6 yr later
18585	W	F		Skull		Tumors		Excision, 1915; 1916	Cancellous bone	Recurred
18506	W	M	22	Fibula, head	1	Tumor	Broad exostosis	Resection, October 1915	Cancellous bone	Well over 14 yr
17287	W	M	16	Femur left		Tumor		Excision, April, 1916		7 yr well
17003	W	F	54			Tumor		Excision, February 1914	Cancellous bone; adult cartilage	No improvement 7 yr
16896	W	F	27	Femur lower right	60	Stiffness; pain	Fracture through pedicle exostosis	Excision, December 1914	Cancellous bone; adult cartilage	Discharged well
16882	W	M	30	Os calcis		Pain	Calcaneal spurs	Excision, December 1914	Cancellous bone adult cartilage	8 yr well
16694	W	M	12	Humerus, left	48	Tumor		Excision, December 1914	Cancellous bone; adult cartilage	Discharged well
16491	W	M	48	Big toe, right		Tumors		Excision, November 1914	Cancellous bone adult cartilage	Discharged well
16420	W	M		Fibula, upper		Tumor after typhoid fever	Broad exostosis	No operation		
16296	W	M		Femur	84	Tumor; pain				
16273	W	M	21	Astragalus		Tumor		Excision, September 1914	Cancellous bone; adult cartilage	Discharged well

Table 3. Benign Osteochondromas (Exostoses) (Continued)

Pathologic No.	Race	Sex	Age	Location	Duration, mos	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
15933	W	M	49	Foot, right	73	Tumor		Excision, June, 1914		Discharged well
15910	W	M	30	Tibia, upper	24	Tumor		Excision, 1914	Adult cartilage; new bone	Well 7 yr; suicide
15603	W	F	20	Toe	30	Tumor		Excision, May 1914	Cancellous bone; adult cartilage	6 yr well
15535	W	M	[illegible]	Femur lower right	72	Tumor	Broad exostosis	Excision, March, 1914	Cancellous bone; adult cartilage	3 yr well
15303*	W	M	[illegible]	Both feet	144	Pain		Excision, January 1914	Cancellous bone; adult cartilage	Discharged well
15022	W	M	48	Scapula, right	1	Pain and muscle atrophy		Excision, December 1913	Cancellous bone in tendon	Well over 16 y
14865*	W	M	34	Second and third lumbar vertebra	12	Pain		Excision, November 1913		Dead
14967	N	F	23	Lower jaw	48	Tumor		Excision, November 1913	Cancellous bone	Discharged well
14744	W	M	15	Femur lower right	60	Tumor; pain	Pedicle exostosis	Excision, October 1913	Cancellous bone; adult cartilage	Discharged well
14671	W	M	29	Os calcis	14	Trauma; tumor		Excision, September 1913	Cancellous bone; fetal cartilage	Well 6 yr lost
14580	W	F	34	Radius, lower right	3	Pain; tumor		Excision, August, 1913	Cancellous bone	Well 9 yr
14343	W	M	[illegible]	Os calcis	84	Pain		Excision, 1913; 1916	Cancellous bone; cartilage, myxoma	Improved 5 yr after recurrence
14331	W	M	18	Fibula, lower left	3	Trauma; tumor; pain		Excision, June 1913	Cancellous bone; calcifying cartilage	Well 6 yr
14249*	W	M	15	Fingers, both hands	156	Tumor; pain		Excision, June 1913	Adult cartilage	Well over 16 yr
14175	W	M	22	Femur, lower right	3	Tumor	Pedicle exostosis	Excision, May 1913		Discharged well
13503	W	M		Tibia, lower	24	Tumor	Pedicle exostosis	Excision, 1913	Cancellous bone; adult cartilage	Discharged well
13723				Finger		Tumor		Amputation, 1913	Cancellous bone; adult cartilage	Discharged well
13383	W	M	24	Os calcis	18	Pain; tumor		Excision, October 1912	Cancellous bone; adult cartilage	Discharged well
13770	W	M	23	Humerus, upper left	180	Tumor	Broad exostosis; cartilaginous cap	No operation		Unchanged
13493*	N	M	9	Humerus and femur	48	Multiple tumors; pathologic fracture of femur	Central and periosteal changes in in femur	Excision and curettement of humerus	Cartilage; no myxoma	Well [illegible] yr
11967	W	F	68	Os calcis	36	Trauma; tumor		Excision, August, 1911	Cancellous bone in tendon	Well 10 yr; died of other causes
11801	W	M	16	Femur lower	1	Pain		Excision, June, 1911		Well 16 yr.; died of other causes
11334	W	F	26	Femur lower	192	Trauma; tumor		Excision, February 1911		Discharged well
11063	W	M	42	Skull, multiple	288	Trauma		No operation		Well 11 yr

10123	W	F	7	Metacarpal		Tumor		Excision, November 1909	Cancellous bone; adult cartilage	Discharged well
9916	W	M	23	Os calcis	48	Pain		Excision, 1909		Discharged well
9480	W	F	27	Femur, lower	180	Tumor	Pedicle exostosis	Excision, August, 1909		Discharged well
9720	W	M	[illegible]	Humerus	48	Tumor		Excision, May 1909	Cancellous bone; adult cartilage	Well 13 yr
9674	W	M	12	Cervical spine	30	Pain	Rounded exostosis	Excision, May 1904	New bone; fibrous tissue	Well 25 yr
9802	W	F	27	Femur, lower	36	Tumor; pain		Excision, March, 1909		Discharged well
9039	N	M	23	Femur, lower	24	Tumor; limitation of motion	Pedicle exostosis	Excision, June, 1909	Cancellous bone; adult cartilage	Discharged well
7881	W	M	24	Femur, lower	9	Trauma; pain; tumor		Excision, January 1907	Cancellous bone; adult cartilage	Well 23 yr
6815	W	F	40	Humerus, upper right	4	Tumor	Pedicle exostosis	Excision, October 1905		Well 24 yr
6367	W	M	30	Ilium, crest	6	Tumor	Fuzzy broad exostoses	N operation		Well 13 yr
6251	N	F	12	Femur, lower, left	36	Tumor; pain		Excision, April, 1906	Cancellous bone	Discharged well
6252	N	M	21	Femur, lower, right	144	Tumor; pain	Rounded exostoses	Excision, May 1906	Cancellous bone; adult cartilage	Well 16 yr
6023	W	F		Tibia, upper		Tumor		Excision, December 1904		Discharged well
5957	N	M	24	Tibia	49	Trauma; ulcer				
5813	W	M	14	Tibia, shaft	36	Tumor; pain		Excision, October 1904		Dead other causes
5646	W	F	12	Toe, phalanx		Tumor		Excision, July 1901		Discharged well
5468	W	M	24	Tibia, lower		Tumor		N operation		Unchanged
5535	W	F	45	Upper jaw	168	Tumor; pain	Rounded exostosis	Excision, May 1904	Cancellous bone; fibrous tissue	Recurred 9 yr later
5302	N	M	18	Os calcis	8	Gonorrheal arthritis	Calcaneal spurs	Excision, March, 1904		Discharged well
4419	W	M	60	Femur, shaft	229	Trauma; tumor		Excision, 1909		Well 20 yr
[illegible]	W	M	11	Scapula, right	43	Tumor		Excision, August, 1901		Well over 25 yr
2748	W	F	17	Jaw, left, lower	36	Tumor		Excision, 1895		Well 3 yr later
2583	W	F	44	Ischium	120	Pain	Pedicle exostosis	Excision, 1893	Cancellous bone; adult cartilage	Discharged well
2514	W	F	13	Scapula, left	48	Tumor		Excision, 1900		
2497	W	F	15	Sternum	24	Pain		N operation		Unchanged
2071	W	M	41	Tibia, subcavity	84	Pain				Well 9 yr later
1852	W	M	23	Big toe		Tumor		Excision, 1892		Discharged well
1622	W	F	10	Radius	1	Multiple tumors		Excision, 1892		
1257	W	F	25	Femur, lower	180	Tumor; pain	Pedicle exostosis	Excision, 1891		
7821	W	M	46	Scapula	60	Tumor				
400	W	M	30	Humerus, upper	18	Pain; tumor		Amputation, 1894		Dead other causes 7 yr later
743	N	F	41	Skull, frontal	96	Trauma; tumor		Excision, 1890		
739	W	M	20	Jaw, lower angle	36	Tumor		Excision, 1890		Well 8 yr later
890	W	M	33	Femur, lower	5	Trauma; tumor		Excision, 1891		
802	W	F	11	Tibia, head	6	Tumor; pain		Excision, June, 1890		Well 33 yr
440	N	F	18	Scapula	448	Tumor		Excision, 1890		

TABLE 3. BENIGN OSTEOCHONDROMAS (EXOSTOSES) (*Continued*)

Pathologic N	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
15922	W	M	42	Foot, right	72	Tumor		Excision, June 1914		Discharged well
15910	W	M	29	Tibia, upper	24	Tumor		Excision, 1914	Adult cartilage; new bone	Well 7 yr; suicide
15903	W	F	20	Toe	36	Tumor		Excision, May 1914	Cancellous bone; adult cartilage	6 yr well
15535	W	M	18	Femur lower right	72	Tumor	Broad exostosis	Excision, March, 1914	Cancellous bone; adult cartilage	2 yr well
15203*	W	M	31	Both feet	144	Pain		Excision, January 1914	Cancellous bone adult cartilage	Discharged well
15022	W	M	46	Scapula, right	1	Pain and muscle atrophy		Excision, December 1913	Cancellous bone in tendon	Well over 16 y
14965*	W	M	34	Second and third lumbar vertebrae	12	Pain		Excision, November 1913		Dead
14967	N	F	30	Lower jaw	45	Tumor		Excision, November 1913	Cancellous bone	Discharged well
14744	W	M	18	Femur lower right	60	Tumor; pain	Pedicle exostosis	Excision, October 1913	Cancellous bone; adult cartilage	Discharged well
14671	W	M	29	Os calcis	14	Trauma, tumor		Excision, September 1913	Cancellous bone fetal cartilage	Well 6 yr., lost
14590	W	F	34	Radius, lower right	3	Pain; tumor		Excision, August, 1913	Cancellous bone	Well 9 yr
14342	W	M	43	Os calcis	84	Pain		Excision, 1913; 1916	Cancellous bone; cartilage myxoma	Improved 5 yr after recurrence
14331	W	M	15	Fibula, lower left	3	Trauma; tumor; pain		Excision, June 1913	Cancellous bone; calcifying cartilage	Well 6 yr
14349*	W	M	15	Fingers, both hands	156	Tumor; pain		Excision, June, 1913	Adult cartilage	Well over 16 yr
14175	W	M	22	Femur, lower right	3	Tumor	Pedicle exostosis	Excision, May 1913		Discharged well
13803	W	M		Tibia, lower	24	Tumor	Pedicle exostosis	Excision, 1914	Cancellous bone adult cartilage	Discharged well
13722				Finger		Tumor		Amputation, 1913	Cancellous bone; adult cartilage	Discharged well
13383	W	M	24	Os calcis	18	Pain; tumor		Excision, October 1913	Cancellous bone; adult cartilage	Discharged well
12770	W	M	22	Humerus, upper left	180	Tumor	Broad exostosis cartilaginous cap	No operation		Unchanged
12493*	N	M	9	Humerus and femur	48	Multiple tumors pathologic fracture of femur	Central and periosteal changes in femur	Excision and curettement of humerus	Cartilage; no myxoma	Well 10 yr
11947	W	F	65	Os calcis	36	Trauma; tumor		Excision, August, 1911	Cancellous bone in tendon	Well 10 yr; died of other causes
11861	W	M	16	Femur lower	1	Pain		Excision, June, 1911		Well 16 yr; died of other causes
11334	W	F	23	Femur lower	108	Trauma; tumor		Excision, February 1911		Discharged well
11063	W	M	42	Skull, multiple	288	Trauma		No operation		Well 11 yr

10123	W	F	7	Metacarpal		Tumor		Excision, November 1909	Cancellous bone; adult cartilage	Discharged well
9916	W	M	23	Os calcis	48	Pain		Excision, 1909		Discharged well
9990	W	F	27	Femur lower	180	Tumor	Pedicle exostosis	Excision, August, 1909		Discharged well
9730	W	M	30	Humerus	48	Tumor		Excision, May 1909	Cancellous bone adult cartilage	Well 13 yr
9673	W	M	13	Cervical spine	30	Pain	Rounded exostosis	Excision, May 1909	New bone fibrous tissue	Well 25 yr
9602	W	F	27	Femur lower	36	Tumor pain		Excision, March, 1909		Discharged well
9029	N	M	23	Femur lower	24	Tumor; limitation of motion	Pedicle exostosis	Excision, June, 1908	Cancellous bone; adult cartilage	Discharged well
7851	W	M	24	Femur lower	8	Trauma; pain, tumor		Excision, January 1907	Cancellous bone adult cartilage	Well 23 yr
6615	W	F	40	Humerus, upper right	4	Tumor	Pedicle exostosis	Excision, October 1905		Well 24 yr
6367	W	M	30	Ilium, crest	6	Tumor	Fuzzy broad contour	No operation		Well 12 yr
6291	N	F	12	Femur lower left	36	Tumor; pain		Excision, April, 1905	Cancellous bone	Discharged well
6253	N	M	21	Femur lower right	144	Tumor; pain	Rounded exostosis	Excision, May 1905	Cancellous bone; adult cartilage	Well 16 yr
6022	W	F		Tibia, upper		Tumor				Discharged well
5957	N	M	24	Tibia	48	Trauma; ulcer		Excision, December 1904		
5813	W	M	14	Tibia, shaft	36	Tumor; pain		Excision, October 1904		Dead other causes
5646	W	F	13	Toe, phalanx		Tumor		Excision, July 1904		Discharged well
5468	W	M	21	Tibia, lower		Tumor		No operation		Unchanged
5426	W	F	45	Upper jaw	168	Tumor; pain	Rounded exostosis	Excision, May 1904	Cancellous bone; fibrous tissue	Recurred 9 yr later
5362	N	M	18	Os calcis	5	Gonorrheal arthritis	Calcaneal spurs	Excision, March, 1904		Discharged well
4412	W	M	52	Femur shaft	228	Trauma; tumor		Excision, 1902		Well 20 yr
3823	W	M	11	Scapula, right	48	Tumor		Excision, August, 1901		Well over 23 yr
2746	W	F	17	Jaw, left, lower	36	Tumor		Excision, 1895		Well 3 yr later
2393	W	F	44	Ischium	120	Pain		Excision, 1895		Discharged well
2914	W	F	13	Scapula, left	48	Tumor	Pedicle exostosis	Excision, 1900	Cancellous bone; adult cartilage	
2497	W	F	16	Sternum	24	Pain		No operation		Unchanged
2071	W	M	51	Tibia, tuberosity	24	Pain				Well 9 yr later
1642	W	M	22	Big toe		Tumor		Excision, 1893		Discharged well
1622*	W	F	10	Radius	j	Multiple tumors		Excision, 1893		
1287	W	F	23	Femur lower	160	Tumor; pain	Pedicle exostoses	Excision, 1891		
7821	W	M	46	Scapula	60	Tumor				
900	W	M	30	Humerus, upper	18	Pain; tumor		Amputation, 1894		Dead other causes 7 yr later
743	N	F	41	Skull, frontal	96	Trauma; tumor		Excision, 1890		
730	W	M	20	Jaw lower angle	36	Tumor		Excision, 1890		Well 3 yr later
690	W	M	23	Femur, lower	5	Trauma tumor		Excision, 1891		Well 22 yr
602	W	F	11	Tibia, head	6	Tumor; pain		Excision, June, 1890		
440	N	F	18	Scapula	448	Tumor		Excision, 1890		



FIG. 13. (No. 35720) Roentgenogram showing a typical exostosis in the upper end of the tibia near the insertion of the quadriceps tendon. The outgrowth is continuous with the normal bone beneath and a distinct bursa overlies the exostosis. The presence of a calcareous bursitis makes this complication clearly visible. This is the exostosis bursata of the older authors.

common and justifiable habit of clinicians to be influenced in favor of making the diagnosis of a benign condition when the history of the tumor extends over a number of years, as it does in most cases of exostoses. It is therefore important to call attention here to the fact that despite the duration of the disease, malignant change marked by exacerbation in the symptomatology may take place in these lesions, and in such cases the most important evidence is the growth rate in the tumor and not the duration of the disease In making a diagnosis of malignancy it is helpful to know that the malignant change is most frequent after the age of 30 and that care must be taken to rule out an acute bursitis or inflammation in the overlying soft parts (Fig 13)

The location of the lesion is an important factor in leading to its discovery although tumors in any area may be accidentally disclosed by a roentgenographic examination made for other reasons. Exostoses occurring about the pelvis are particularly prone to exist without giving any clues to their presence.

Stiffness in the adjacent joint after prolonged use of the limb is not an infrequent symptom Apparently the stiffness or limping is brought on through irritation by the bony tumor to the overlying ligaments and tendons during the use of the limb Rest



FIG. 14. (No 39602) Exostosis of the pedicle type at the site of the adductor tubercle in the lower end of the femur Note the widened metaphyseal region near the outgrowth and the extension of the pedicle in the direction of the pull of the adductor magnus muscle



FIG. 15 Roentgenograms of unusual osteochondromas. (*Left*) Osteochondroma arising from the posterior surface of the eighth rib. (*Right*) Osteochondroma of the os calcis. Both of these patients have remained well following excision.

e affected part brings early relief from symptoms.

ysical examination of the patient with oses is usually negative except for local ngs. In only two instances in this series there a positive Wassermann reaction efinite syphilitic history and the blood t and urine examinations were uni ly negative. In a definite percentage he cases in which some systemic or ditary factor is operative the lesions be multiple. Arthritis associated with orrheal infection may be a complicating or in some instances.* A familial dis- known as hereditary deforming chon- lysplasia may be responsible. This last up of hereditary multiple exostoses is ussed subsequently in Chapter 3

ocal examination of the tumor reveals a firm swelling securely attached to the underlying bone. There is little or no tenderness to be made out on deep pressure. The soft parts overlying the tumor are most often freely movable unless there has been undue irritation with inflammation. At times, the mass will feel much larger than might be expected from its size in the roentgenogram. If the bulk of this mass is firm and rubbery a large proportion of cartilaginous tissue that is invisible in the roentgenogram will be found. Such a predominance of cartilage is most frequent in children. If fluctuation is obtained, an overlying bursa containing fluid may be responsible, this bursa being occasionally visualized in the roentgenogram (Fig 13) when there are calcareous deposits in the synovial fluid of the sac.

ROENTGENOGRAPHIC FEATURES

The roentgenographic appearance of an exostosis is determined by its mode of attachment to the underlying bone and the size and character of its overlying cartilag

While the osteophytes common to hyper ...ic arthritis are not included in this study se- ...d cases of calcaneal spurs in gonorrheal ar ...s (in which the microscopic changes were in- ...guishable from osteochondromas) have been ...ded to emphasize the point that the tissue of ...in, and not the etiologic agent, is the deter ...ing factor in the histology of these neoplasms.

inous cap If the attachment to the under lying bone is by means of a tapering ped icle the exostosis is usually referred to as the pedicle type (Fig 14) If the attachment to the bone is represented by a broad area which merges imperceptibly into the shaft of the bone, the exostosis is generally referred to as the broad base or sessile type (Fig. 16) Occasionally the exostosis may be attached to the underlying bone by an extremely narrow pedicle, or one which has become fractured and resorbed so that no apparent bony connection is visible in the roentgenogram. This, however is the exception.



Fig. 16 (No. 42142) The roentgenographic appearance of the broad-base type of exostosis. In this case there is a bulging of normal bone over a wide area at what is normally the site of the tibial tuberosity There is little calcification in the thin overlying cartilaginous cap

The structure of the pedicle or base of the exostosis is one of its characteristic roentgenographic features This bony attachment is composed of bone differentiated into cancellous and cortical zones, and these zones are both merged imperceptibly with the normal cortical and medullary portions of the bone beneath. There is some evidence to indicate that the entire pedicle or base of the exostosis is not of true tumor origin but represents an outpouring of normal osseous tissue through a gap in the overlying periosteum. The most important feature, therefore, in the roentgenographic appearance of the exostosis when differentiating it from sarcoma is not the bony attachment but the neoplastic cartilaginous cap

This cartilaginous cap of the exostosis may vary from a small, nearly invisible overlying zone (Fig 16) to a large calcifying

cauliflower mass (Fig 17) If this cartilaginous mass is small, or if it is definitely or faintly outlined with calcified material, there need be no hesitancy in making the diagnosis of a benign lesion. When, however the cartilaginous mass is large and ill defined on its outward margin, and when its calcified areas are being resorbed and present a granular appearance, and when, in addition these more translucent zones are secondarily invading the bony base or pedicle, malignancy is to be suspected, and the symptomatology is to be carefully checked (Fig 18)



FIG. 17 (No. 39064) Osteochondroma at the lesser trochanter of the upper end of the femur in which the neoplastic cartilaginous cap predominates in the form of a calcifying cauliflower mass. Although this growth bulges into the soft parts in many directions, the absence of bone destruction in the underlying tuberosity and in the base of the exostosis indicates a benign lesion. This patient was last reported well in 1940 14 years after this observation. This picture should be compared with Figure 18.

In addition to the roentgenographic appearance of the exostosis itself it is always useful to examine the adjacent metaphyseal region of the involved bone. A widened metaphyseal zone as pointed out by Jansen is typical of fully developed or mild degrees of hereditary chondrodysplasia, a diffuse disease of the skeleton with which benign, single or multiple exostoses are often associated.

Exostoses occurring on the shaft side of the long bones, particularly in the region of the thigh or elbow must be differentiated in the roentgenogram from myositis ossificans traumatica In ossifying myositis the ossifying mass has often no attachment



FIG. 18. (No. 37868) Osteochondroma at the greater trochanter of the upper end of the femur which has undergone secondary malignant change Note the granular and hazy outward margin of the calcified cartilaginous cap and the bone below the trochanters. The patient was a white man, aged 29 who died eight years after the first symptoms with metastases. The roentgenogram was taken three months before death. Compare with Figure 17

to, and is not continuous with, the underlying bone. It presents a typical parallel laminated appearance and lacks the characteristic cartilaginous cap so often seen in benign exostosis. The definite history of trauma followed in about six weeks by a hard mass of stationary size typical of myositis ossificans traumatica is an important clinical distinction

GROSS PATHOLOGY

At operation or after excision an exostosis has the appearance of a firm, lobulated tumor overlaid by a smooth and glistening fibrous surface (Fig. 20) If the tumor is cut into, the shiny surface is readily seen to be composed of two layers, one a thin fibrous envelop not exceeding 1 mm. in thickness, and the other a translucent, cartilaginous zone, generally less than 1 cm. in thickness. Beneath these two layers the bulk of the tumor mass, which is composed of cancellous bone is found. The relative proportion of cartilage and bone in the usual exostosis is subject to variation. While it is true that the cartilage composes only a thin cap in most of the tumors, still in other growths this more primitive type of tissue may constitute so much of the bulk



FIG. 19 Cartilaginous exostosis in a child of eight years. The roentgenogram depicts the translucent "half moon" defect in the broad, osseous base, characteristic of these unripe osteochondromas of childhood. This is the ecchondroma of the older literature. It is a benign lesion.



FIG. 20. (No 40040) Outward appearance and sectioned surface of an excised exostosis. On the outward surface is seen the glistening membrane to which fibers of the tendon have been attached at nodular points. On the cut surface, the thickness of the cartilaginous portion overlying the cancellous bone is plainly visible.



FIG. 21 (No. 28392) Gross specimen showing the nodular and lobulated cartilaginous portions in an exostosis in the upper end of a fibula in a white girl, aged 14. A cure was effected by resection.

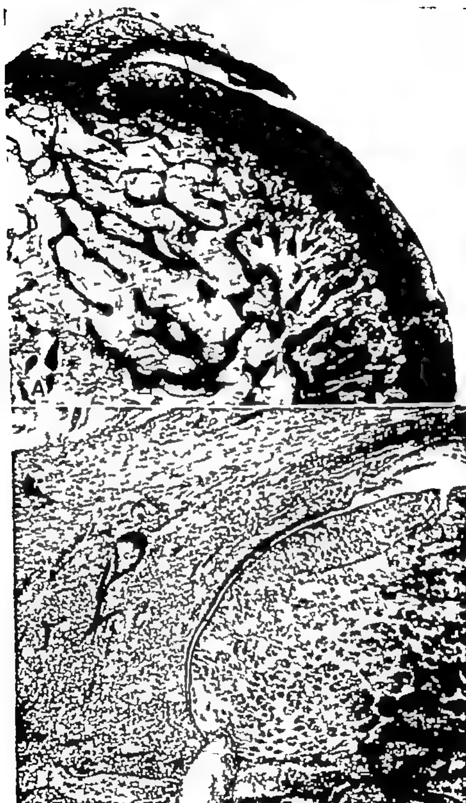


FIG. 22. (No. 288[illegible]) [illegible]oscopic studies showing the relationship of a benign exo[illegible] [illegible] adjacent tendon. (A) shows a low magnification of [illegible] with a piece of overlying tendon partially encircl[illegible] the c[illegible]laginous cap. The tendon is seen in the upper left-hand [illegible] beneath the cartilaginous rim is a large area of cancell[illegible] bone enclosing fatty bone marrow. (B) shows a



FIG. 23 (No. 28770) Low power photomicrograph of the normal articular surface of the lower radius. The picture shows the joint cartilage the zone of provisional calcification and the underlying normal bone Most of the perichondrium overlying the cartilaginous surface was lost in making the preparation. Note how the transition from cartilage to bone follows the order shown in the exostosis in Figure 25

that these tumors have been described as periosteal chondromas. The greater the percentage of cartilage in the tumor the more frequently it is composed of knotty masses or definite lobules (Fig 21)

The relationship of the muscular attachments entering the tumor areas is most significant. The tendon ends are often blended imperceptibly with the thin fibrous membrane which overlies the cartilaginous cap Even under the microscope this merging of the tendon with the tumor capsule can

higher magnification taken from the area marked in (A) The cellular primitive connective tissue embedded in the tendon is giving rise to cartilage on the one hand and to bone on the other

be seen (Fig. 22) and on this relationship hinges largely the conception of the histogenesis of these tumors.

ones adjacent to the normal underlying bone, shows a characteristic transition from fibrous tissue to cartilage to bone. The most



FIG. 24. (No 28770) Higher magnification of area marked in Figure 23 at the point of reflexion of the joint capsule. At this point there persists primitive precartilaginous tissue giving rise to cartilage This is a normal growth center

MICROSCOPIC FEATURES

The typical microscopic picture of the osteochondroma seen under low magnification is shown in Figure 25 The tumor passing from the superficial layer to the deeper

superficial layer is generally a hyalinized connective tissue, very poor in nuclear material, which caps the tumor over its outward surface. At points in this cap, there are islands of more cellular connective tis

sue which, when put under high-power magnification show many small spindle-shaped nuclei arranged in a syncytial fashion, resembling myxoma. Beneath the fibrous layer is a zone of hyaline cartilage. In the regions where the connective tissue is cellular there are numerous fetal cartilage cells, but these small areas of fetal cartilage are insignificant beside the major portion of chondral tissue which is of the adult variety and resembles in all respects the typical chondroma. In its deeper portions this cartilage undergoes calcification and abutting on the zone of calcified cartilage, laminated bony spicules are to be found. This laminated adult bone is cancellous in structure with a generous amount



Fig. 25 (No 26392) Photomicrograph from the specimen shown in Figure 21 The overlying fibrous portion of the exostosis in the upper right hand corner is the direct continuation of fibers of an adjoining tendon. The entire histogenesis of the neoplasm can be traced in this picture At the upper margin is the primitive connective tissue which is the mother substance of the tumor This tissue is giving rise to a small amount of fetal cartilage beneath which there is much normal adult cartilage calcifying in its deeper layers. Beneath this there is a protrusion of normal adult bone enclosing a small amount of fatty marrow Between the bone and calcifying cartilage is a row of giant cells derived from the bone marrow

of fatty bone marrow between its trabeculae. Osteoblasts are generally not applied to the spicules, only here and there has this bone the coarse fibrous structure typical of new bone formation

The entire microscopic picture is preponderantly one of quiescence the varying histologic zones appearing like the stratified deposits of an obliterated sea It is only



FIG. 26. Roentgenograms of osteochondromas of tibia and ilium. (*Top*) Anterior and lateral views of tibial osteochondroma. (*Bottom*) Osteochondroma projecting from wing of ilium

in isolated zones that evidence of active proliferation persists. This is in keeping with the clinical characteristics of these tumors, which are slow in their growth and mild in the symptoms provoked. These isolated areas of cell proliferation, however are the points most important for the study of the histogenesis of these neoplasms and must be considered in more detail. They also supply a focus for the malignant change that occasionally occurs in these tumors.

In the areas of cellular fibrous tissue, the capsule dips into the tumor dividing it into lobules (Fig. 27) These penetrating strands of connective tissue give rise to groups of fetal cartilage cells and also, in most instances, to small amounts of new bone. It is therefore plainly evident that the mother substance of the cartilaginous portion of these tumors is the precartilaginous connective tissue found indenting the tumor from its periphery Although to this early connective tissue must also be ascribed the function of new bone formation, it is by no means certain that the large amount of adult bone comprising the bulk of the exostosis is derived from this same mother substance The entire mass of this adult bone is so intimately related with the shaft of the underlying normal bone that it appears to be arising as a protrusion of the shaft, rather than as a deposit of the small amounts of osteogenic tissue found in the neoplastic portions of the cartilaginous cap. If this interpretation is correct in the histogenesis of these tumors, it becomes necessary to explain not only the origin of the cartilaginous growths that form the cap of the exostosis, but also to account for the independent proliferation of normal bone beneath, which constitutes the pedicle or base of the osteochondroma.

HISTOGENESIS

The close simulation of the usual exostosis to a normal articulating surface of bone as well as the relationship that the location of the tumor generally has to points of tendinous attachments, focuses attention on the embryology of these normal structures. In both normal tendons, which attach directly to bone (Figs. 29 and 30) and in normal joints at the reflexion of the joint capsule, proliferating zones apparently acting as normal growth centers may be found. In these proliferating centers early cartilage cells derived from young fibroblasts may be seen (Figs. 29 and 24) and occasional areas of ossification, a transition of tissues typical of the osteochondromas. The occurrence of such proliferating zones in normal tendon ends was first observed by Kölliker* in 1853 (Fig 28) and similar transitional zones are typical of tenosynov-

* Kölliker A.: Manual of Human Histology London, Sydenham Society 1853–1854, Vol. 1, p. 251



FIG. 27 (No 42142) Photomicrograph of a benign osteochondroma or exostosis. In the one microscopic field, there are shown three distinct zones, the first, a narrow rim of connective tissue (of the precartilaginous type) at the outer margin, dipping into the tumor to form lobules second, a middle area of cartilage, which is gradually undergoing calcification, and third, normal cancellous bone enclosing a small amount of fatty bone marrow

itis associated with calcareous bursitis (Harbin*) In the development of joint mice, the studies of Henderson and Jones† demonstrated that loose cartilaginous bodies may undergo ossification in the synovial membrane (Fig 33) showing again the relationship of the histologic transi

* Harbin, R. H: Deposition of calcium salts in the tendon of the supraspinatus muscle Arch. Surg. 18 1491, 1929

† Jones, H. T: Loose body formation in synovial osteochondromatosis, with special reference to etiology and pathology J Bone & Joint Surg. 6 407 458, 1924

tions typical of exostosis to articular and periarticular structures.

In normal bones the growth centers at the epiphyseal line contain cartilage and, since the time of Virchow misplacement or other abnormalities of these disks have been blamed for the origin of exostoses.

Keith first pointed out that failure of the broadened epiphyseal plate to undergo remodeling might account for the exostosis through a persistence at its edge of the cartilage of the epiphyseal plate. This theory received support through the work of Bisgard. He produced displacement of the distal epiphyses of rabbits by removing segments of the shaft of the radius. In 7 out of 12 rabbits exostoses developed from avulsed fragments of epiphyseal cartilage Some traumatic exostoses may arise in this way

Muller in an autopsy performed in a case of multiple exostoses found persisting islands of cartilage in the periosteum. He believed that exostoses arise from such periosteal rests. Mahorner subscribes to the view of Keith. Jaffe believes that both Keith and Muller have described important phases of the histogenesis of osteochondromas and supports a combination of both theories. We believe that these theories contribute more to an understanding of multiple exostoses than of the solitary variety

The solitary osteochondromas, however are not related histogenetically to the bone proper nor to the epiphyseal line as a rule, but rather to the articular and periarticular

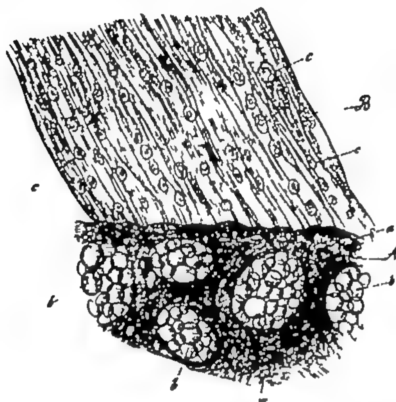


FIG. 28 This drawing reproduced from Kölliker depicts cartilage cells (c) in the end of the Achilles tendon (B) which attaches directly to the bone of the os calcis (A) This is the first known record of the discovery of precartilaginous connective tissue giving rise to cartilage in the substance of a tendon. (After Kölliker Human Histology London, Sydenham Society 1853 Vol. 1 p 251)

structures already cited. This deduction is confirmed by a comparative study of the embryology of the joints, periarticular structures and bone

Both the bones and joints begin their differentiation from a single type of mesenchymal derivative. This mesenchymal derivative is a simple condensation of embryonic connective tissue which forms at the site of the future skeleton (Fig 8, p 31) It represents the precartilaginous state of the future skeleton and is known as blastema Whereas the blastema of the future skeleton differentiates rapidly into cartilage so



FIG. 29 (No 46035) Low-power photomicrograph showing the attachment of the extensor carpi radialis longus to the metacarpal in a white man, aged 31 (the hand was amputated for a sarcoma of the soft parts occurring in another portion of the hand) The illustration shows the persistence of precartilaginous connective tissue with the proliferation of cartilage forming a junction between the bone in the upper portion of the picture and the tendon in the lower This embryonic tissue of union between tendon and bone at the normal sites where chondromyxosarcomas arise refutes the current misconception in regard to the origin of such tumors by a process of dedifferentiation.

as to form an entire cartilaginous skeleton (with exception of the membranous bones) at an early date in embryonic life, the so-called extraskeletal blastema, which is des-



FIG. 30 Low power photomicrograph showing precartilaginous connective tissue with cartilage formation at the insection of the quadriceps tendon into the tibial tuberosity in a young dog.

tined to form joints and the attachments of certain tendons and ligaments, lags behind and goes through a somewhat different cycle of changes. By mucoid regression in this extraskeletal blastema, the joint cav ities and certain bursae are formed, and where this dense connective tissue overlaps and extends beyond the bone, the joint capsule, the ends of ligaments and tendons and the synovia are differentiated.

Thus, the joint cavity the joint capsule, the synovia, the ends of various ligaments and tendons and associated bursae are all derived from this one mother substance. This extraskeletal blastema tissue in all of its derivatives retains at points the power of cartilage and bone formation throughout life. But unlike the skeletal cartilage differ



FIG. 31 Roentgenogram of an osteochondroma of the thumb The tumor is arising at the insertion of the adductor pollicis.



FIG. 32. Photomicrograph of the same osteochondroma.

entiated from this blastema at an earlier stage, this type of chondral tissue does not undergo active resorption by giant cells in its calcified state, but becomes converted more directly into permanent bone. Both giant-cell activity and marrow formation are sparse in these growths.

Therefore, on embryologic grounds, as well as by site and localization, the osteochondromas because of the histologic cycle from fibrous tissue to cartilage to bone which they show in their growth zones or cartilaginous caps, must be histogenetically related to the extraskeletal blastema or the forerunner of articular and periarticular structures.

In tendons such as the Achilles, the quadriceps at its attachment below the knee and the adductor magnus fastening above the medial condyle of the femur union is established, not with the periosteum, but directly to bone These tendons have their osseous ends formed, not by ordinary fibrous tissues, but by extraskeletal blastema (Fig 35) and since the periosteum is normally lacking or deficient at such points, the underlying bone lacks a limiting membrane and grows out in the form of a normal bony protuberance to meet the tendon. Such outgrowths of bone are normal occurrences and are known as the adductor tubercle, the tibial tuberosity and so on. The entire tuberosity which provides for such ligamentous attachment, however is not derived from the underlying bone but is added to more indirectly from preceding cartilage formed from the blastema in the ligament or tendon. Both the shaft of the bone and the end of the tendon thus co-operate in the formation of the tuberosity

Therefore, the normal structures at the site of a future exostosis, which must be superseded or distorted in order for tumor formation to take place are (1) the end of a tendon or ligament formed from blastemal tissue and destined to aid in the formation of its own bony attachment (2) an underlying zone of normal bone without periosteal covering destined to form an outgrowth or attachment point in the skeleton (3) a margin of periosteum surrounding the zone which eventually is to form a sleeve or cuff about this zone.

The origin of an osteochondroma or exostosis at such transitional zones depends on abnormal variations in some one of the foregoing factors. If both the zone of cartilage in the tendon end and the bony outgrowth of the underlying bone are normally

Macewen, W The Growth of Bone Observations on Osteogenesis. An Experimental Inquiry into the Development and Reproduction of Diaphyseal Bone Glasgow James Maclehose & Son, 1912.

balanced and eventually overlaid by periosteum, an osteochondroma will not form. If however the periosteum surmounts only the outgrowth of the underlying bone and fails to blend with the fibrous tissue of the tendon the growth of the cartilaginous center in the fibrous attachment of the muscle will not be properly limited, and a tumor results. In such an event, the cartilaginous zone in the tendon overgrows the protuberance of normal bone, overlapping the periosteum and forming a typical exostosis.

It is clear from the foregoing facts that osteochondromas are compound growths, since the underlying osseous pedicle is composed of normal bone which has a deficiency in its periosteal covering, while the overlying cartilaginous cap arises independently from precartilaginous connective tissue in the end of a tendon or ligament and provides the truly neoplastic elements of the tumor



Fig. 33 Low-and high-power photomicrographs showing the development of cartilage in tags of synovial tissue within the joint cavity This illustrates the histogenesis of the so-called joint mice occurring in osteochondromatosis of the knee joint and proves the power of cartilage formation residing in the primitive connective tissue of the synovial membranes. (Jones, H. T J Bone & Joint Surg 6: 407 1924)

ETIOLOGY

From a consideration of the histogenesis involved in tumors of the osteochondroma group the multiplicity of possible etiologic factors becomes apparent. In congenital exostosis, in which these tumors are frequently multiple and often hereditary there is undoubtedly a tendency to variation in the periosteal apertures about the zones where bony protuberances normally arise. That this congenital variation affects the periosteum and underlying cortical bone primarily as well as the cartilaginous zone of growth in the ligaments and tendons is evidenced by the diffuse metaphyseal widening so often seen in this form of so-called hereditary deforming chondrodysplasia. Apparently the rim about the periosteal deficiency is either unusually wide or abnormally inactive or both, permitting the underlying bone to protrude in an unusual manner



FIG. 34. Progressive growth in immature cartilaginous exostosis. (*Left*) Roentgenogram showing the appearance of the lesion at the age of 12 years. (*Right*) Appearance of the lesion 3 years later The tumor is benign and must be differentiated from osteogenic sarcoma.



FIG. 35 Low-magnification of a longitudinal section of the lower leg of a human embryo The future skeleton is preformed in cartilage The entire tibia is shown, the cartilage of which is undergoing calcification in the pinched, mid shaft region. At (A) is seen the insertion of the quadriceps tendon (embedding the patella) into the future tuberosity of the tibia. The dense black connective tissue of the tendon is persisting precartilaginous connective tissue. At (B) is seen the dense primitive connective tissue in the region of the insertion of the Achilles tendon. Note the persistence of this dense connective tissue within the future knee joint

In regard to the exostosis of inflammatory origin, such as the calcaneal spurs in gonorrheal arthritis, the fault in this instance is not a deficiency in the activity of the adjacent periosteal cuff but rather an overstimulation of the cartilaginous center in the tendon where the infection has directly initiated an increased growth activity Despite the unorthodox procedure of classifying these infectious osteophytes with the neoplasms of the osteochondroma group microscopic distinction between the two is impossible, and histogenetically as has just been shown, there is a common basis of origin (Fig 36)

The important consideration in the etiology of all exostoses is the persistence of extraskeletal blastema at the tendon's end, at the site of origin. The skeletogenic tissue at this site is primitive mesenchyme, which can differentiate and does differentiate in three separate directions: to fibrous tissues, to cartilage and to bone. The difference between these three end products of skeletogenic differentiation is entirely in the cement substance elaborated, i.e., collagen for fibrous tissue, hyalin for cartilage, and mineralized ossein for bone. At the site of normal bony protuberances the differentiation of fibrous tissue predominates; in the abnormalities giving rise to exostoses, the differentiation of cartilage and bone predominates.

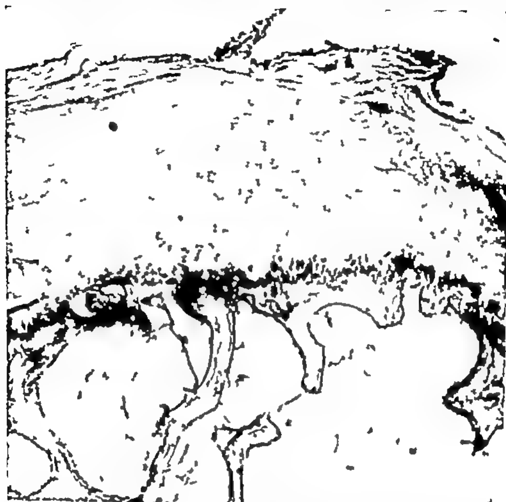


Fig. 36 (No. 34167) Low power photomicrograph of a calcaneal spur in a white man, aged 39, giving a history of gonorrhea 13 years previously followed by polyarthritis for a number of years, which at first affected all the joints but which finally localized at both ankles. In the picture there is seen the overlying connective tissue continuous with the tendon, the zone of cartilage and the underlying bone typical of all exostoses. Compare this with Figure 27.

Over the past sixteen years, since the first edition of this book, detailed clinical histories have been taken by the authors on a large series of cases. The number of patients who observe the growth of the exostosis during adolescence is a striking feature, and it may also be observed that the exostosis makes itself manifest during the year when the maximum increase in height occurs. In many cases, this has amounted to from six

to eight inches of growth in a year When one bears in mind the fact that the exostosis always grows in the direction of the muscle pull and when one considers, also that exostoses may arise subperiosteally in any long bone where a large tumor of the soft parts exerts special traction by its weight on the periosteum, it appears logical to assume that traction or tension on the tendinous attachment during rapid skeletal growth is an etiologic factor

TREATMENT AND PROGNOSIS

The foregoing analysis of the histogenesis and etiology of exostoses has an important bearing on the treatment and prognosis of the disease. Ordinarily these lesions are benign and represent merely a readjusted imbalance between two normal phases of growth. Operative intervention is not called for since in the usual exostosis the periosteum and underlying cortical bone succeed eventually in "hemming in" the cartilaginous cap except at the point where the fibrous portions of the tendon or ligament perform an identical function. However operative removal may become necessary because of the interference by the tumor with the function of the surrounding muscles in the use of the adjacent joint. When the location of the tumor is such that repeated injuries result in the formation of a bursitis, the consequent painful lesion warrants excision.

In the removal of such an exostosis, a more careful dissection is warranted than is usually given such tumors. The zone of periosteum overlying the adjacent normal bone about the pedicle or base should be carefully delimited and marked out by the knife and laid back. The base or pedicle should then be chiseled through and the tumor lifted off the underlying bone. The fibers of the tendon entering the tumor zone should then be incised above the cartilaginous zones which are frequently embedded in them. After the growth has thus been removed, care should be taken to provide for the reanchoring of the strands of the tendon and to suture the adjacent fascia and muscles over the rift in the periosteum to aid in the restoration of the normal cortex when healing occurs.

Ordinarily the usual exostosis, when operated on, is accorded no such systematic treatment. The tumor is chiseled away piecemeal in a careless fashion the surgeon neglecting the relationship of the adjacent tendons to the tumor The result is that recurrences of such benign exostoses are by no means rare (5 per cent of this series) and when recurrence does not take place, the adjacent cortex often reforms in an irregular and troublesome manner

While many exostoses do not require operation and cures are commonly effected in those with aggravated symptoms by simple surgical removal, there is a third group in which both the prognosis and the treatment are an entirely different problem. This is the group of benign osteochondromas which undergo secondary malignant change In the present series of cases, malignancy arose in about 5 per cent of these benign exostoses or osteochondromas. This is a far higher percentage than is generally conceded, but the reason for this increase in the percentage of malignancy in the present series is due to the care with which they were studied.

It is not sufficient to follow up the cases of benign exostoses and to find out in which of them the patients subsequently die of sarcoma developing in the original lesion. The usual benign exostosis which comes under the observation of the physician or surgeon is removed, and this removal usually eventuates in healing so that the possibility of malignancy is obviated. In patients discharged without treatment or who have recurrence after removal there is, of course, the possibility of malignancy But there is also a still larger group of cases that never come under the observation of any physician until malignant change has occurred. To determine this third group it is necessary to examine carefully the roentgenograms and specimens in all cases in the



FIG. 37 Roentgenograms and photomicrograph of benign osteochondroma arising at the adductor tubercle of the femur The sections show the junction of cartilaginous (*left*) and osseous tissues.

osteogenic sarcoma group and to isolate those cases which show evidence of arising in a previous osteochondroma It is this third group of cases (Tables 12 and 13) in which most of the osteochondromas terminating in sarcoma were found.

In view of this fairly large percentage of cases with malignant change, the question arises whether or not the removal of an exostosis is warranted as a preventive measure. Such a wholesale removal of these growths is not favored, but attention is called to the need of following cases in which operation has not been performed and of informing the patient to return at once if he observes any unusual increase in the growth or an aggravation of symptoms. In addition, tumors which are discovered in the roentgenogram in and about the pelvis or about the spine should be removed or followed by repeated roentgen examinations because their location makes any increase in size dangerous to the patient. These growths do not respond to irradiation.

SUMMARY

The largest group of benign tumors arising from precartilaginous connective tissue in the skeleton are the benign osteochondromas or exostoses. These neoplasms are most common near the ends of the long bones of patients between the ages of 10 and 25 years and form a bony skeletal outgrowth surmounted by cartilage. While a great number of these osteochondromas escape clinical observation, because of the absence of symptoms the majority give evidence of their presence by painless swelling of the bone or by stiffness with rheumatic pains in the neighboring joint, the average duration of such mild symptoms being slightly over five years. The distinctive diagnostic features of this group of lesions are the base or pedicle of normal bone protruding through a periosteal gap and the more or less overflowing neoplastic cartilaginous cap This structure is visible in the roentgenograms as an osseous outgrowth differentiated into cancellous and compact portions which merge imperceptibly with identical zones in the normal bone beneath, and as an overlying cartilaginous growth with varying degrees of calcification and an occasional superimposed bursa containing fluid or calcareous material.

A similar structure can be traced under the microscope Going from the most outward layer to that next to bone, there is visible first an insignificant primitive connective-tissue membrane merging with the

adjoining tendons, second, a zone of cartilage of the normal adult type undergoing calcification in its deeper layers, and third, a zone of normal laminated bone differentiated into cancellous and cortical zones enclosing islands of fatty bone marrow. Histogenetically these tumors are considered to be an exaggeration of a normal bony protuberance intended for the anchoring of an important tendon. At such a junction nature provides normally for a protuberance of bone bulging through a gap in the periosteum to meet an adjoining tendon, which co-operates in the formation of the attachment by cartilaginous ossification within the substance of the tendon. An exostosis represents a failure in the accurate approximation of the tissues entering into such a junction the cartilaginous center in the tendon persisting in the form of primitive connective tissue, proliferating in excess, and the protuberance of normal bone beneath extending to form a pedicle or base.

Cases of single exostoses without symptoms may be left untreated but should be watched by repeated roentgen examination, since they may undergo secondary malignant change, particularly after the age of 30. Simple excision usually suffices to cure those osteochondromas producing pain or dysfunction.

Unusual and Atypical Osteochondromas. Atypical osteochondromas may be encountered at special ages and at special sites. In children, between the ages of 6 and 12, particularly in the deltoid tubercle of the humerus, the base of the exostosis may appear as an osseous platform and the uncalcified cartilaginous cap forms a half moon, indenting or set into the osseous base. This type of exostosis has been referred to in the older literature as a periosteal chondroma, ecchondroma and cartilaginous exostosis. Actually it is an immature osteochondroma in which the cartilaginous cap is chiefly uncalcified. If left alone, such a growth usually will mature as a typical benign exostosis. Surgical intervention is not indicated, but, if undertaken, the cartilage does not transplant or acquire malignant potentialities at this age. These immature exostoses must not be confused with exostoses in adults in which the cartilage is proliferating and invading the base of osseous tissue. In such cases, in adults, the appearance on roentgen examination may be similar but the prognosis in regard to metastases and recurrences is grave (Figs 19 and 34).

In adults, osteochondromas may be found in the coracoid process of the scapula. The author has observed four such cases. In every case, surgical intervention was followed by disaster. The cartilaginous tissue in these four cases of exostoses of the coracoid process transplanted and proliferated. In three cases, the patients died of metastases. The fourth patient has been living for five years after a shoulder-girdle amputation but now has pulmonary metastases (Fig 96, p 157).

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3

Multiple Exostoses or Hereditary Deforming Chondrodysplasia

In the foregoing discussion of osteochondromas or single exostoses, an analysis was made which emphasized, not the cartilaginous or the osseous portions of these tumors, but instead, their derivation from a precartilaginous connective tissue concerned with periarticular functions. Although this tissue is visible only in remnants at the periphery of these tumors, it is nevertheless the mother substance of the cartilaginous mass that has received so much attention by other authors. This tendency to emphasize the chondral substance of these tumors instead of their *connective-tissue origin* particularly when they assume the form of multiple cartilaginous exostoses or hereditary deforming chondrodysplasia, has been the cause of much confusion in the attempts to interpret the nature of this multiple skeletal disease.

Hereditary deforming chondrodysplasia (a term used by Ehrenfried) denotes a distinct clinical form of exostoses in which the multiple occurrence of such tumors in a single patient is accompanied by numerous other skeletal deformities, such as bending and shortening of the bones and widening and irregularity of their metaphyseal ends. This form of the disease known in the literature under many different terms is congenital and is usually discovered in childhood. The hereditary factor is extremely prominent and has been traced through as many as four or five generations. The mode of transmission is direct but somewhat variable, and apparently both males and females may transmit the disease. Stocks and Barrington found, in tracing 727 cases from 163 family trees, that the father was responsible in 73 per cent of the cases for the inheritance and the mother in 27 per cent. It has been described in both whites and Negroes, but is rare in the Negro race. The fundamental basis of the congenital disturbance is obscure, but deficiencies in the periosteum and a tendency for the perichondrium *to persist and to function as such,* (Müller) together with precartilaginous connective tissue about the joints, seem to be responsible for most of the deformities.

CLINICAL FEATURES

Although the disease is active throughout the developmental period of skeletal growth, the actual age of observation varies according to the time when the physician is first consulted. Usually the patient comes under observation between the ages of 5 and 20 but the disease has been reported as early as the age of 2 years and as late as 80 The deformities affect only the bones derived from cartilage and are most marked in the bones of the forearm and leg, although the femur and humerus rarely escape. Most of the exostoses are found in the cortical region of the bone, resulting in a

See Chap 2, p. 77

widening of the shaft at these points and giving rise at their base to areas of increased or decreased density In addition to the outward projections at these points,



Fig 38. (No. 28246) Case of congenital multiple exo toses showing fusion between the lower end of the radius and the lower end of the ulna. Note the bending and distortion of the bones of the forearm and the undeveloped state of the distal end of the ulna.

there may be an inward growth resulting in the formation of chondromatous foci in the cancellous bone. The last named have often been mistaken for cysts of the bone in the roentgenograms. Where two adjacent bones are affected, as the radius and ulna or the tibia and fibula, fusion may occur between the expanded and distorted ends (Fig. 38) the lesser bone (fibula or ulna) usually suffering arrested development.

In well-developed cases, the outstanding symptomatology relates to the deformity or so-called "family mark," which consists in shortening of stature and crookedness of the arms or legs As the disease progresses, one or more of the osteochondromas, because of continued growth, will impinge on important structures, causing pain and dysfunction One of such common disturbances is a paraplegia or local paralysis. Exostoses about the spine may result in either a spastic or a flaccid paraplegia, while local growths in the region of the knee by pressure on the peroneal nerve may give rise to paralytic foot drop In rare instances, an aneurysm has developed as a result of constant trauma to an adjacent vessel.

Variability characterizes the more marked symptoms of the disease During the youth of the patient, painful growths may continue to arise, to decrease or to become arrested after the patient reaches maturity While the deformities tend to become stationary in adulthood, exacerbation of symptoms may be produced by local irritation to an underlying growth. As pointed out for single exostoses, an increase in the severity of symptoms after the age of 30 in a previously dormant osteochondroma may be the first sign of a malignant change. Jaffe found chondrosarcoma in 11 per cent of his 28 cases. Bennett and Berkheimer reviewed the literature relating to chondrosarcoma as a complication of this disorder

Unless neurologic manifestations a present, examination of the patient usual shows few systemic features of clinical i terest other than those relating to the skel ton. Unlike chondrodystrophia fetalis, the is no alteration of the physiognomy and r deformity of the head, but congenital anom alies, such as a deficiency of the bladd sphincter may be present. The bones the trunk are usually not markedly involve by the disease, although exostoses affectin the spine and ribs are occasionally recorde

ne extremities there is a tendency for irly symmetrical bilateral involvement, ough unequalness in the length of either osteochondromas in which malignancy may be suspected may exceed the size of a child's head.



FIG. 39 (No. 28539) The bones about the knee joint in a case of hereditary deforming chondrodysplasia. In addition to the numerous exostoses note the widening of the metaphyseal ends of the bone which gives to the lower end of the femur and upper end of the tibia a characteristic squared-off appearance.

rms or legs is not rare. Full extension is often limited, and there is bowing of the forearms and often of the legs. Deformities of the hands and feet, particularly in the phalanges, are common. Definite hard and knotty outgrowths attached to the bone may be palpated, usually near the ends of the bones but occasionally near the region of the midshaft. The quiescent growths are less than the size of a fist, but progressive

ROENTGENOGRAPHIC FEATURES

In the roentgenograms taken of this condition, numerous typical osteochondromas, involving the metaphyseal region of the long bones, are found. These outgrowths may appear in clusters about a given region and beneath the point of these exostoses, the shaft of the bone is widened and the cortex is thinner than normal. The exostoses



FIG. 40 (No 25432) Roentgenogram of hereditary deforming chondrodysplasia or multiple exostoses. Besides the multiple exostoses shown in the picture this patient had widening of the metaphyseal ends of the bones, curvature in the bones of the forearms and legs, and deformities in the cortical zone at many points.

vary in configuration, some being of the pedicle type, others a cauliflowerlike growth with a broad base, and still others rounded, elevated areas near the deformed end of the bone (Fig 40) All of them grow and point in the direction of the muscular pull.

In the ulna or fibula, bending is usually marked, and there is an arrest of growth showing shortening and failure of the epiphyseal ends to develop properly (Fig 38) In the ulna, it is usually the low of the bone which is deficient, and i this region that fusion with the radiu takes place. In the fibula, the upper most frequently affected, and syn with the tibia may result. Although t tire end of a bone, such as the lower the ulna, may be distorted by thes growths and the thinning of the corte the foamy area in the base of the ex may resemble a cyst, true cysts of th such as those seen in osteitis fibros not been recorded in the present serie to our knowledge these central growt rare and are always chondromas.

This is one of the easiest conditions entire bone-tumor group to diagnose roentgenogram. The three salient fe determining the diagnosis are the f tion of multiple exostoses of the pedi broad base type, the widening of the physeal ends of the long bones (Fi and the deformity with bending and i of the ulna or fibula, in the forearm The appearance of the bones about th is typical (Fig. 39) The lower end femur is squared off and the exostose jecting therefrom are directed upw the direction of the muscle pull. The end of the tibia is similarly distorte outgrowths in this instance pointing ward. The upper end of the fibula panded and often fused with the e the tibia

The possibility of malignancy in conditions is a much disputed point. I lignancy occurs, it is never generaliz multiple in focus, but arises in a osteochondroma, and for this reason in no way from the possible mali change discussed under single exo (Fig 41)

Apart from the cases of typical he tary deforming chondrodysplasia wit outspoken manifestations, there are sional nonhereditary cases in which se cartilaginous tumors may affect a bone or several widely separated on the same side of the body Rarely

instances are observed in which multiple chondromas of the hand are associated with exostoses in the arm or another long bone. More frequently several exostoses in a single region of one bone have been observed. Associated with such a nest of lesions, the same metaphyseal widening is seen as in hereditary deforming chondrodysplasia and there may also be bending and deformity of the bone. Such cases are best referred to as multiple exostoses or simple chondrodysplasia and represent a transitional group of lesions midway between single osteochondromas on the one



FIG. 41. (No 28246) Malignant change in an osteochondroma of the transverse process of the fourth lumbar vertebra in a white woman aged 41 who suffered from hereditary deforming chondrodysplasia. There were multiple exostoses in the bones of the legs and arms. The sister and brother of the patient suffered from similar defects, as did an uncle on the father's side. The infiltrating character of the lesion is shown.



FIG. 42. Antero-posterior and lateral views of osteochondroma of the femur. Note the lesion in the fibula. There were multiple exostoses and central cartilaginous rests in all the long bones in this case.

hand and multiple exostoses of the hereditary deforming chondrodysplasia type on the other.

GROSS PATHOLOGY

Adequate study of the gross pathology of these lesions is difficult, owing to the scarcity of material. Since the disease is not fatal and operation, when performed, is restricted to a single lesion, a detailed study of many bones has rarely been made. In general the pathologic process of the local growths is the same as that described for the single osteochondroma. The important points of difference are the multiplicity of the tumors, the frequency with which cartilaginous masses are found embedded in the medullary and subcortical regions of the bone beneath the exostoses and the bending and distortion of the long bones, particularly the ulna and fibula (Fig. 38).

The widening of the metaphyseal region and the distortion of the bone beneath the site of the exostoses are among the most interesting features of this condition of the

skeleton. Many explanations have been ad vanced to account for these peculiarities, most of them relating the conditions either to a generalized disease such as rickets, syphilis or tuberculosis, acting on the epi physeal line, or to a failure of the metaphy



FIG 43 (No 19339) Gross specimen from a case of hereditary deforming chondrodysplasia after a resection of the upper end of the tibia and upper end of the fibula. The uncut surface (A) shows the numerous cartilaginous outgrowths and synostosis between the fibula and tibia. The cut surface (B) shows islands of chondromatous tissue extending into the epiphyseal and met aphyseal regions of the cancellous bone.

sis to become modeled into a normal shaft because of some inherent and hereditary defect. The first group of explanations relat ing to the epiphyseal line and originating with Virchow have been gradually abandoned. The other group of explanations relating to the metaphysis are more current but are mostly theoretical without a true pathologic or embryologic basis.

Another of the more striking deformities is the stunting of the growth of those bones that do not bear direct strain or weight, such as the ulna and fibula. The curious way in which these two bones are outstripped in size and growth by their neighbors, the radius and tibia, affords an important clue to the pathologic picture of the disease.

Microscopically the duplication in the multiple exostoses of the histologic picture, described under single osteochondromas, indicates that the histogenic processes described in connection with those lesions also apply to the more diffuse form of this skeletal condition.

HISTOGENESIS

The formation of a single exostosis is an exaggeration of a normal bony protuber ance. It is formed when developmental disturbance of the periosteum about the tuber

osity of a bone occurs with proliferation of the precartilaginous connective tissue of the tendon. This suggests that in hereditary deforming chondrodysplasia, in which so many of these tumors are present a similar disturbance occurs. In its earliest state, the bulk of the periosteum is in reality perichon drium, a tissue identical with the precar tilaginous connective tissue about the joints and in the ends of the tendons. If there is an arrest of development and a tendency for this precartilaginous tissue to persist not only in periarticular regions but also at points in the periosteum, the bones of car tilaginous origin will be affected through out. This probably occurs in multiple exostoses. Not only do the periarticular points of primitive connective tissue act as sources for these cartilaginous growths, but, in ad dition, the periosteum at many points does not develop as such but is replaced by in sufficient amounts of the more primitive perichondrium.

The failure of the periosteum to develop adequately or rather its tendency to lag behind its normal rate of differentiation, has a multiplicity of effects on the bone beneath. Among other things, the cortex does not achieve its full thickness, owing to the absence of an adequate subperiosteal layer of osteogenic tissue provided with fully developed osteoblasts. Also this perichondrol tissue is more responsive to the stress of rapid growth. For this reason multiple outgrowths appear in the juxta-epiphyseal regions of the long bones where growth is most rapid.

PROGNOSIS AND TREATMENT

The prognosis for life in these cases is good, but there is no adequate form of treat ment except operation for correction of deformities after the growth period has ceased. Most of the deformities, such as shortening of stature and unequal length of the bones of the extremities, give no indication for treatment, but exostoses causing neurologic manifestations, dysfunction in the use of limbs or injury to vessels should be promptly excised.

In two cases in this series secondary ma lignant change occurred in these cartilag inous growths, resulting in death from chondromyxosarcomas. Other such cases with malignant change have been reported from time to time in the literature The treatment of such sarcomatous growths is discussed in Chapter 6 on secondary chon dromyxosarcoma

OSTEOMAS OSSIFYING FIBROMA OSTEOID OSTEOMA, ETC.

Direct ossification in fibrous tissue oc curs in the membranous bones of the skull, the frontals, parietals upper maxillae, etc. (see Chaps. 20 and 21) Osteoblasts forming in a proliferation of connective tissue surround spicules of osteoid and osseous material, resulting in spongy and later compact bone. This mode of ossifica tion is also observed in the formation of the cortex in the intracartilaginous bones. Pathologically it is seen in the long bones as a healing reaction about bone cysts and fibrous dysplasia (see Chaps. 10 and 12) in low-grade osteomyelitis and in myositis ossificans.

In the membranous bones of the skull and jaws, typical benign tumors, osteomas, may form as a result of this type of ossification. These growths occur usually in children or young adults in the frontal or parietal bones of the skull and in the bony walls of the frontal or maxillary sinuses. They are about one-fourth as common as the osteochondromas just discussed and are rare in the long bones.

The more rapidly growing osteomas are composed of cellular fibrous tissue in which small, round osteoid bodies are formed. This type of rapidly growing osteoma is often mistaken for fibrosarcoma (Chap. 21) It is properly classed as an ossifying fibroma The more slowly growing tumors of this type form spongy bone and are classed as spongy osteomas. In the most highly differ

entiated osteomas, compact bone is formed, giving rise to ivorylike swellings classed as eburnated osteomas.

The ossifying fibromas, spongy osteomas and eburnated osteomas are benign tumors which do not warrant mutilating operations. They are often complicated by trauma or infection. Because their distribution is restricted to the membranous bones a detailed consideration of these growths has been reserved for the chapter on tumors of the jaws and skull (see Chaps. 20 and 21)

In the recent literature, benign fibro-osseous tumors of the endochondral bones have received special emphasis, under the term of fibrous dysplasia. These relatively rare lesions of the long bones have been considered by some (Schlumberger) as identical in character with the ossifying fibromas of the membranous bones. The fact that they are not true ossifying neoplasms is indicated by their inability in their more mature stages to lay down compact ivorylike masses in the long bones, akin to the eburnated osteomas in the skull. A detailed discussion of fibrous dysplasia has been reserved for the chapters which treat of osteitis fibrosa and bone cysts.

Myositis ossificans, occurring in the immediate vicinity of the long bones, and usually separated by an interval from bone by the fibrous layers of periosteum, deserves consideration as an ossifying fibroma of skeletogenic tissues. In ossifying lesions of this character an intermediate cartilaginous stage is often seen under the microscope. Its similarity to a callus after a fracture and its definite relationship to trauma justify its classification as an extra-osseous callus rather than a true neoplasm. A fuller discussion of myositis ossificans is found in Chapter 16.

Osteoid osteoma, a small tumor with imperfectly formed osteoid spicules, occurring in vascular mesenchyme, is an entity described by Jaffe in 1935 These lesions rarely exceed one centimeter in diameter and may occur in cancellous bone or intracortically. They are described in Chapter 16

SUMMARY

Multiple exostoses or hereditary deforming chondrodysplasia is a congenital disturbance of the perichondium and affects markedly the growth of the bones derived from cartilage. Tags of perichondrium in the tendon ends proliferate to form cartilaginous and bony outgrowths. Disturbances and deficiencies in the periosteum in the metaphyseal regions lead to widening of the metaphysis and inhibition of bone growth. Roentgenograms taken of this condition disclose numerous osteochondromas involving the metaphyseal regions of the bones, widening of the metaphysis and variation in the length of the bones. The regions most frequently affected are the forearm and leg, the bones of which may become fused. Bending in the extremities is frequent. Central chondromas may be formed. Microscopically tumors excised from the bones in this condition are osteochondromas or chondromas.

The prognosis for life is good, but there is no adequate form of treatment except operation for correction of deformities after the growth period has ceased. With such multiple skeletal involvement, secondary malignant change in these cartilaginous growths may occur

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4

Chondromas or Chondromyxomas

A fairly common type of cartilaginous tumor designated hero as benign central chondroma, resembles the exostoses histologically but has not the same periosteal location or the same preponderantly osseous structure that is characteristic of the base or pedicle of the osteochondromas.

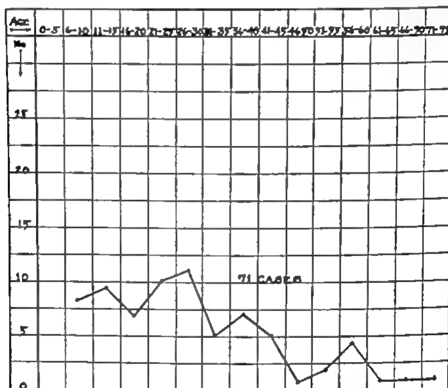


CHART 8 Showing age incidence of benign chondromas occuring in the small and large bones of the skeleton.

The typical chondroma is a benign lesion occurring in the small bones of the hands and feet or about the ribs and spine in patients between the ages of 20 and 30 In the phalanges of the hand where this tumor is most frequently located, the growth produces a central rarefaction in the affected bone. This in the roentgenogram is visible as an expanded and cystic area within a shell of cortical bone. These chondromyxomas have been described as occurring commonly in the long pipe bones and about the pelvis in either a central or a periosteal location. However in such locations these tumors are rarely of central

origin. Of those of periosteal origin described as chondromas, the majority are in reality osteochondromas with a large cartilaginous cap they have been grouped under the exostoses (Tables 2 and 3) It is also essential to point out here that many of the chondromas growing to tremendous size described as benign lesions in the literature, are slowly growing chondromyxosarcomas arising secondarily in benign exostoses. This type of tumor is subsequently discussed under the heading of secondary chondrosarcoma." (Chap. 6.)

CLINICAL FEATURES

In a series of 113 chondromyxomas (Tables 4 through 7) males and females were about equally affected the majority of the patients were white and only four such lesions were recorded in Negroes. The curve of age distribution is shown in Chart 3 and resembles the benign osteochondromas except that the peak of incidence is a decade later between 20 and 30 instead of 10 and 20 years. The predominant location, as shown in Figure 44, is in the bones of the hands and feet, 60 of 110 lesions

TABLE 4 CHONDROMAS IN SMALL BONES

Pathologic No.	Race	Sex	Age	Location	Duration mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
62933	W	M	29	4th phalanx					Cartilage cells of adult type with signs of degeneration	Well 2 yr
62648	W	M	46	4th phalanx	4	Fracture	Rarefaction	Curettage	Adult hyaline cartilage	Well 4 yr
61736	W	M	41	3d, 4th phalanx phalanges left foot	236	Rapid growth, recent	Benign chondroma	Curettage	Adult hyaline cartilage	Lost
60266	W	F	32	Metacarpal	144	Recent growth, rapid		Excision	Adult and fetal cartilage	Lost
60250	W	M	15	Phalanx	6	Trauma	Rarefaction, protuberance, fracture	Curettage cautery	Precartilaginous tissue and fetal cartilage	Well 9 yr
59376	C	M	31	Metacarpal, 3d phalanx		Injury pain, pathologic fracture	Rarefaction, widening fracture	Splinted		Lost
57732	W	M	38	1st phalanx, 4th finger			Decreased density chondromyxoma			Well 11 yr.
57344	W	M	13	Proximal phalanx 4th finger		Tenderness, swelling, injury	Typical osteochondroma			Well 12 yr.
54474	W	F	38	Left foot	12			Amputation of toes		Well 3 yr
52178	W	F	21	Finger	12			Excision	Chondromyxoma	Well 6 y
52156	W	F	16	Toe				Curettage	Chondromyxoma	Well 6 yr
51432	W	F	48	Right toe				Curettage	Chondromyxoma	Well 1 yr
49430	W	M	[illegible]	Great toe				Curettage	Chondroma	Well, 1 y
49034	W	M	23	Metacarpal	48			Excision	Chondroma	Well, 6 yr
47624	W	M	43	Finger	24	Pain, tumor		Excision	Chondroma	Well, 4 y

TABLE 5. BENIGN CHONDROMYXOMAS IN SMALL BONES OF THE HANDS AND FEET

Pathologic No.	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
45163	W	F	13	Multiple fingers and toes	Congenital	Tumor	Multiple rarefied areas	Excision, 1929	Myxoma cartilage; bone	Discharged well
40494	W	F	20	Phalanx, ring finger		Tumor		Curetted, 1929		Discharged well
37758	W	F	10	Phalanx right little toe	2	Tumor; pain	Central rarefied area	Curetted, 1927	New bone fetal cartilage	Discharged well
38538	W	F	30	Phalanx, right thumb		Pathologic fracture	Central expanded rarefied area	Curetted, 1927		
38160	W	F	18	Phalanx, right little finger	72	Trauma; tumor		Curetted, 1926	Cancellous bone; adult cartilage	Discharged well
37112	W	F	30	Metacarpal, right	48	Fracture; tumor		Resection, 1926	Fetal cartilage; myxoma	Well 8 yr
36880	W	F	32	Phalanx, middle finger	60	Trauma; tumor; pain	Central and cortical rarefied area	Curetted, 1926	Adult and calcifying cartilage	Well 4 yr
36458	W	F	13	Phalanx, right forefinger	96	Trauma; tumor; pain	Central expanded rarefied area	Curetted, 1925	Cancellous bone; adult cartilage below myxoma	Well 4 yr
36408	W	F	19	Phalanx, right finger	72	Trauma with repeated fracture	Rarefied area with fracture	Irradiated, 1924; operation		Well 6 yr
35943	W	M	48	Thumb, right	24	Trauma with dislocation	Ossified tumor in tendon	Excision, 1925		Discharged well
35638	W	F	30	Middle phalanx, thumb		Pathologic fracture	Translucent area with ossification	Roentgen therapy 1924		Healing after 2 yr
35504	W	M	9	Thumb and forefinger left	36	Trauma	Multiple periosteal and central translucent tumors			Unchanged 6 yr after
35365	W	M	19	Metacarpal little finger		Tumor	Central rarefied area	Irradiation, 1924		Some improvement 6 mo. later
35288	W	M	37	Phalanx, index finger	14	Trauma, pain	Central expanded rarefied area	Amputation, 1924		Discharged well
34286	W	F	13	Phalanx, ring finger	24	Tumor	Central rarefied area	Observed, 1923; no operation		Well 7 yr
34048	W	F	40	Finger left middle		Tumor	Central rarefied area	Excision, 1923	New bone; adult cartilage	Well 7 yr
33153	W	F	19	Phalanx, ring finger	12	Tumor	Central and cortical rarefied area	Irradiation, 1922		Unimproved lost
33071	W	M	23	Phalanx, toe	14	Trauma; tumor	Central expanded rarefied area	Amputation, 1923	Fetal cartilage; myxoma; new bone	Well 6 yr
33848				Great toe		Tumor	Sclerosed bone			
32793	W	M	14	Phalanx, middle finger	24	Trauma; tumor; pain	Central expanded rarefied area	Curetted, 19[illegible]		Well 6 yr
30836	W	M	6	Phalanx, fourth finger right	24	Tumor	Central and periosteal translucent area	Excision, 1922	Dense myxoma; fetal cartilage	Discharged well

20572	W	F		Phalanx, index finger	13	Tumor pain	Sesamoid bone (?)	No operation; observed, 1922		Well 8 yr
20647	W	M	30	Phalanx, thumb	24	Trauma; tumor	Central rarefied area	No operation; observed, 1922		Unchanged
27604	W	F	35	Phalanx, ring finger	168	Trauma pain	Central rarefied area	No operation; observed, 1922		Well 6 mos; lost
27228	W	F	21	Phalanx, fore-finger	96	Trauma; tumor; pain	Central rarefied area	No operation		Unchanged
29245	W	F	10	Fifth, metacarpal	36	Trauma; tumor; pain	Central rarefied area	Curetted, 1921		Well 8 yr
27229	W	F	30	Phalanx, thumb		Tumor	Central rarefied area, cortex roughened	Amputation, 1921	Fetal cartilage; myxoma	Well 8 yr
29010	N	M	10	Phalanx, big toe	3	Tumor	Central expanded rarefied area	Amputation, 1921	Hyalinized cartilage	Well 7 yr
29464	W	M	22	Phalanx, index finger	60	Tumor	Central rarefied area	Curetted, 1921	New bone; fetal cartilage; myxoma	Well 9 yr
28353	W	M	27	Third, metacarpal	84	Heal fracture	Central expanded rarefied area	Curetted, 1921	New bone; fetal cartilage; myxoma	Well 9 yr
27698	W	F	48	Phalanx, ring finger	24	Pain; tumor	Periosteal translucent area	Excision, 1921	New bone; fibrous tissue	Discharged well
26622	W	M	30	Phalanx	48	Trauma; tumor; pain	Periosteal translucent area	Excision, 1920	New bone; calcified and fetal cartilage	Well 9 yr
26230	W	F	75	Phalanx, little finger	48	Tumor	Central expanded rarefied area	Amputation, 1920	New bone; fetal cartilage; myxoma	Well 8 yr; dead 1928, heart disease
25644	W	M	70	Third metacarpal		Limitation of motion	Multiple rarefied areas	Amputation	Adult and calcifying cartilage	Discharged well
25254	W	M	22	Phalanx, third toe, left	36	Trauma with pathologic fracture	Central expanded rarefied area	Amputation, 1918		Well 1 yr; lost
23958	W	M	35	Phalanx, little finger	48	Trauma; tumor; pain	Periosteal translucent area	Excision, 1918	New bone; calcified and fetal cartilage; myxoma	Discharged well
20944	W	F	25	Phalanx, ring finger	12	Tumor	Central expanded rarefied area	Curetted, 1919	Adult and calcified cartilage	Discharged well
16564	W	M	33	Metacarpal, middle finger	168	Trauma, tumor	Periosteal translucent area; new bone	Excision, 1924	Cancellous bone; adult cartilage	Well 10 yr
15597	W	M	63	Phalanx, ring finger	240	Trauma; tumor	Central rarefied area	Amputation, 1914		Well 14 yr
14480	W	F	15	Third metacarpal	12	Trauma; tumor		Resection, 1912; excision, 1913	Fetal cartilage; myxoma	Well 8 yr after recurrence
12208	W	F	30	Phalanx, index finger	336	Trauma; tumor		Curetted, 1911		Discharged well
9630	W	F	22	Phalanx, little finger	60	Tumor		Excision, 1907	Fetal cartilage; myxoma	Well 13 yr
6802	W	F	40	Phalanx, middle finger	12	Tumor		Amputation, 1901	Fetal cartilage; myxoma	Well 3 yr; lost 1930
4520	W	F	24	Phalanx, ring finger		Tumor		Excision		Discharged well
720	W	M	56	Phalanx, toe	224	Trauma; tumor		Amputation, 1890		Discharged well

TABLE 6. BENIGN CHONDROMAS OF LARGE BONES

Pathologic No.	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
63046	W	M	15	Multiple	10	Swelling		Exploration	Typical chondroma	Well 2 yr.
54310	W	M	31	Humerus clavicle	24			Irradiation		Well 3 yr.
50004	W	F	21	Rib				Excision	Adult cartilage	Well 5 yr.
62976	W	F	50	Clavicle (joint capsule)		Pain, swelling		Resection	Foci of chondromatous tissue within fibrous portion of joint capsule	Well 2 yr
62310	W	M	10	Femur and popliteal space	3	Lump, fever	Sclerosis, lateral condyle of femur calcified masses in popliteal space	Biopsy	Low-grade ossifying cartilaginous tumor rare variety	Dead
61923	W	F	adult	Head of fibula	36	Tumor rapidly extended		Excision	Chondroma extending into muscle and soft parts	Lost
61808	W	M	60	Bridge of nose				Excision	Chondroma with degeneration	
61786	W	M	31	Radius	24	Pain		Resection	Chondroma with fair degree of cellularity	Dead 6 yr. later
61192	W	M		Rib			Chondroma	None		Lost
57350	W	M	25	Ribs	6	Cough, pain	Multiple enchondromata			Living 12 yr.
55110	W	F		Sternum	48	Painless swelling				Well 12 yr.
53690	W	M	15	Multiple chondroma (chondrodysplasia)	6	Shortening left leg, bowing left femur	Benign chondroma			
57404	W	M	19	Rib	216			Excision		Well 4 yr
54933	W	M	41	Scapula				Excision		Dead 2 yr
48113	W	F	27	Femur		Tumor		Excision	Chondroma	Recurrence in 6 yr.
48500	W	M	47	Sternum	2	Tumor		Excision		Dead 3 yr
48414	W	M	49	Rib	24	Tumor		Excision	Chondroma	Well 7 yr.
47332	W	F	54	Tibia	1	Tumor		Excision		Well 4 yr
45498	W	M	27	Rib	24	Pain tumor		Excision		Well 7 yr.
45796	W	M	44	Sternum	24			Irradiation	Cartilage	Well 5 yr
43114	W	M	43	Humerus	36	Pain, tumor		Irradiation		Well 7 yr
42386	W	M	41	Pubis	24	Pain, tumor		Excision		Dead 3 yr recurrence
44890	W	M	7	Ilium	24	Pain, tumor		Excision		Well 11 yr
40106	W	M	38	Pubis	120	Pain		Excision and irradiation	Cartilage	Dead 7 yr
39210	W	M	68	Sternum	60			Irradiation		Dead 4 yr.
38668	W	F	35	Femur lower end	12			Amputation	Chondroma	Well 7 yr

TABLE 7 BENIGN CHONDROMAS IN LARGE BONES

Pathology N	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
24196	W	M	19	Os calcis	60	Pain; tumor	Small rarefied areas	Curetted, 1926		Well 4 yr
42983	W	F	8	Radius, styloid		Tumor		Excision, 1925	Cartilage in tendon	Discharged well
41431	W	M	24	Rib		Tumor		Excision, 1927	Adult cartilage	Discharged well
37744	W	M	35	Os calcis	36	Trauma; tumor; discharging sinus		Drained, 1926; amputation advised		Unimproved
40687	W	M	14	Vertebra		Tumor		Excision, 1927	Cartilage	Discharged well
37483	W	F	19	Symphysis pubis	108	Trauma; tumor	Central destruction of bone	Irradiation, 1927		Lost
37931	W	F	36	Sternoclavicular joint	150	Tumor; pain		Excision, 1926	Hypertrophied joint cartilage	Discharged well
37082	W	M	10	Rib, second, left	120	Trauma; tumor	Cystic periosteal shadow	Irradiation, 1926		Well 4 yr., 1930
30709	W	M	7	Femur, left, lower	12	Pathologic fracture, [illegible]	Subcortical rarefied area with fracture	Osteotomy; amputation, 1925	Joint cartilage; bone	Lost, 1925
34502	W	M	53	Sacrum and lumbar vertebra	180	Trauma; pain; tumor	Lobulated mass	Coccyx resected	Myxoma; cartilage	
32152	W	M	43	Sternum	132	Trauma; tumor	Central expanded rarefied area	Observed, 1915; roentgen therapy prescribed		Dead of tumor 1925
32418	W	M	22	Humerus, shaft, left, pathologic	48	Pain; tumor	Central expanded rarefied area, roughened	Amputation, 1922	Cancellous bone; fetal cartilage	Discharged well
30172	W	M	18	First lumbar vertebra	24	Pain	Periosteal translucent area	Excision, 1918	Cancellous bone; adult cartilage	Well 7 yr
29814	W	F	16	Ribs, third and fourth	30	Tumor	Rarefied area	Observed, 1923; no operation		Well 8 yr
26287	W	F	40	Humerus, upper left	12	Tumor		Excision, 6 times, 1915 to 1919; amputation, 1920	Chondroma, adult cartilage	Recurred, well 10 yr after
22047	W	F	30	Rib, third, sternal end		Tumor		Excision, 1918	Adult cartilage	Discharged well
22016	W	F	51	Femur, lower	84	Tumor; pain	Subcortical expanded rarefied area	Excision, 1917	Adult cartilage; hyalinized fibrous tissue	Well 6 yr lost, 1920
19643	W	M	42	Os calcis	12	Pain; tumor	Central rarefied area	Curetting, 1916; amputation, 1919		Recurred, well 6 yr after
18751	W	M	51	Ninth dorsal vertebra	12	Pain		Excision, 1913 and 1918	Cancellous bone adult cartilage	Dead; second operation
17112	W	F	44	Rib		Tumor		Excision, 1913, [illegible], 1914 treated by radium	Adult cartilage; new bone	Well 8 yr; dead of tuberculosis
15396	W	M	40	Sternum, upper	36	Tumor		Partial excision, 1914		Well, 1922
13790	W	M	14	Ulna, head	4	Tumor; pain; stiffness	Translucent periosteal mass	Excision, 1913	Adult and calcified cartilage; myxoma	Well 9 yr
11342	W	M	20	Thigh	48	Tumor; pain	Translucent soft part, shadow	Excision, 1911	Adult cartilage; laminated bone	Well 11 yr
10407	W	F	24	Ribs, third, right	12	Tumor; pain	Translucent expanded area	No operation		
8192	W	M	38	Fifth rib		Tumor		Excision, 1906		Recurred
8111	W	M	56	Os calcis, right	36	Tumor		Excision, 1907	Adult cartilage; myxoma	Recurred in 1 yr
905	W	M	70	Humerus, upper	12	Trauma; tumor; fracture		Amputation, 1895	Adult; fetal cartilage; myxoma	Dead, other causes 13 yr later

occurring in such localities. The ribs and the sternum are next in order of frequency of involvement, and the region of the spine or pelvis is also a common site.

The patient affected with a benign chondroma or chondromyxoma is most often an adult who complains of recurrent soreness in a tumor of stationary or slowly increasing size located in one of the phalanges of the hand or foot. The symptoms are mild and protracted, the course extending on an average over five years. Trauma is often recalled in connection with the appearance of the tumor or with the exacerbation of the symptoms. Neither pain nor swelling is severe, the diameter of the usual tumor being only several centimeters. Multiple involvement is not as frequent as one might infer from the literature In the present series, only six cases of multiple chondromas are recorded, with diffuse involvement in the hand or foot. Longitudinal striae, representing cartilaginous rests, rather than true chondromas may more often be found in roentgenograms of the bones of the fingers or toes. In addition to the nodules, varying from three to ten in the small bones, there was in three of these cases an involvement of a long bone (femur or humerus)

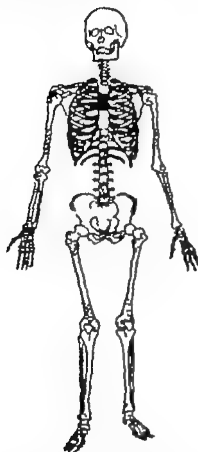


Fig. 44. Incidence of chondromas according to skeletal location. The solid black areas indicate the most frequent sites; the dotted areas the points occasionally involved.

The results of physical examination are usually negative, except for the local changes in the region of the tumor Evidences of specific infections such as syphilis and tuberculosis have not been recorded, nor has bursitis been present in this series. The skin is usually unchanged, and the soft parts are freely movable over the tumor which is firm to palpation, smooth or lobulated to the touch and securely attached to adjoining bone. Pathologic fracture is present in 10 per cent of the lesions.

About the ribs and sternum or when occurring centrally in the long bones, these growths may be of considerable dimensions and larger than an adult fist (Fig 45) In these larger growths a sudden increase in size or malignant change is far more frequent than in the small bones, and recurrence after a primary operation far more likely Malignant change seems prone to occur in these larger tumors, particularly those associated with multiple chondromas in the small bones. Such malignant change (in 25 per cent of our cases) was observed in adults but not in children.

ROENTGENOGRAPHIC FEATURES

In the roentgenogram a typical chondroma is a small, translucent and rarefied area occurring centrally in the shaft of a small bone. The cortex about the lesion is thinned and expanded, inviting pathologic



Fig. 45 (No. 32482) A large chondroma of the sternum observed for over 15 years in a white man, aged 43. This tumor was first observed in 1915 and roentgen therapy was prescribed. Roentgenograms of this lesion are shown in Figure 48. Despite repeated irradiations, mediastinal growth of the tumor produced death in 1935

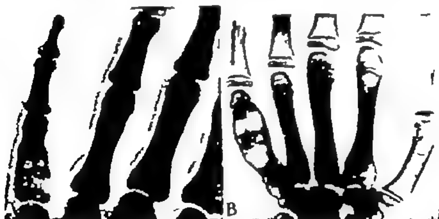


Fig. 46 (A) (No. 29326) shows a central chondroma in the phalanx of the forefinger in a woman 31 years old. The appearance of this tumor followed trauma eight years previously The cortical bone is intact, and the periosteal zones are not involved. (B) (No. 29245) shows a central chondroma occurring in a metacarpal bone in a girl, aged 10 This lesion also followed trauma three years previously but was effectively treated with curetting and has remained well over six years.

fracture. Unlike the osteochondromas, neither new bone formation nor calcification is marked in these small lesions, although trabeculae traversing the tumor (composed of hyalinized fibrous tissue) may be visible in the roentgenogram. Perforation of the bone shell with extension of a translucent shadow into the soft parts is not rare (Fig. 46)



FIG 47 (No 35336) A roentgenogram showing the multiple punched-out areas of gout occurring in the hand of a white man over 50 years of age. Other joints in the body were affected, and recurrent attacks of acute arthritis were present.

The benign chondroma is the most frequent lesion producing central bone destruction in a phalanx. Bone cysts and giant-cell tumors, which may occur in the small bones of the hands and feet and produce a similar picture in the roentgenogram, are more common in the metacarpal and metatarsal bones and are rarer in the phalanges. It is also helpful to bear in mind that multiple giant-cell tumors or bone cysts are practically unknown in the small bones of the extremities. However multiple punched-out areas of bone destruction which are not encapsulated by a shell of cortical bone in these localities may be produced by gout (Fig 47) Metastatic carcinoma and multiple myeloma practically never affect these small bones, unless the rest of the entire skeleton is riddled with the disease.

The majority of the larger tumors of the chondroma class are situated about the sternum at the costochondral junctions or within the body of this bone. In this location they produce a gnarled mass of rubbery consistency which is difficult, because of its location, to visualize clearly in the

roentgenogram. The diagnosis, however can usually be made from the location of the lesion and by the expansion of the bone which occasions no great amount of destruction or erosion. The absence of an infiltrating shadow in the periosteal zones is against the presence of malignancy in these cases (Fig. 48)

True central chondromas of the long bones are extremely rare, and it is doubtful whether such a diagnosis is justified on the basis of the roentgenogram alone. In nearly 3,000 tumors of the bone there are but five well-established cases, and in these, the resemblance is so close to malignancy in the roentgenogram, and the tendency for the lesion to recur and to be cured only by radical operation is so great that there is little practical harm in classing these tumors as forms of chondrosarcoma. Those not experienced may be misled into an erroneous diagnosis of cyst of the bone. Nevertheless, from a scientific standpoint, the possibility of the occurrence of a true central chondroma in the long bones must be conceded, and we have reproduced the illustrations of the roentgenograms of several of these cases. The distinctive roentgen features are expansion of the bone, marking of the translucent areas by lines and particles of calcification and involvement of the periosteal region by peculiar roughened areas (Fig. 49) In these cases roentgenograms of the hands or feet may show longitudinal streakings produced by cartilaginous rests.



FIG. 48. (No 32482) (A) shows the central chondroma of the sternum shown in Figure 45 The roentgenogram was made eight years after the first observation, and although the lesion has grown, the bone shell is still intact and the tumor is outlined by a definite calcified margin. (B) shows the same lesion five years later Note the spotting and granular appearance of the lesion and the extension beyond the bone shell. Because of the stippling and the hazy margins, this picture is suggestive of malignant change Malignant change is very common in chondromas of the large bones after they have persisted for many years in a benign state. This patient died without evidence of metastases. The continually expanding tumor caused death by compression of the heart.

GROSS PATHOLOGY

The outstanding characteristics in the gross specimens of neoplasms composed primarily of cartilage are the lobulated size of the tumor In the small bones, the capsule containing osseous material lends a firmness to the tumor and, in addition, cal cification may aid in solidifying the mass.



Fig. 49 (A) (No 32415) shows a large central chondroma in the shaft of the humerus. The symmetrical nature of the expansion resembles a benign bone cyst, but the multilocular markings of the cavity and the peculiar roughness extending beyond the shell of cortical bone suggest a central chondroma, which is extremely rare in the long bones. (B) (No 22016) shows a rare central chondroma occur ring in the epiphysis of the lower end of the femur This resembles somewhat in appearance a benign giant-cell tumor but it has again the characteristic multilocular appearance of a chondroma.

and gelatinous character of the growth. The tumor is always composed of numerous pockets, marked off by visible fibrous trabeculae, and within these pockets there is a typical translucent and congealed substance of more or less rubbery consistency which under the microscope can be identified as cartilage. Variation in this lobulated and gelatinous appearance depends on the Elsewhere in the large bones, where the tumor attains a greater size, there is a tendency to cystic change in the pockets of the lobules, and these cysts may contain a syrupy fluid which pours from the tumor when it is sectioned (Fig. 50)

The color of the tumor varies from a pearly gray to light yellow Occasionally small foci of hemorrhage may discolor the

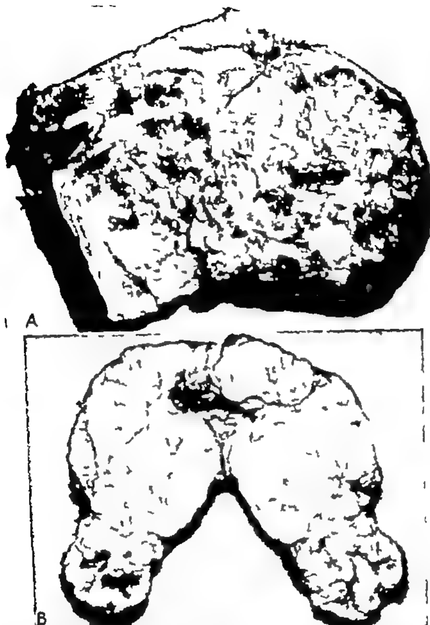


FIG. 50 Gross specimens of two recurrent chondromatous lesions of the large bones in patients who have remained well over five years. (A) (No. 26287) shows a lobulated tumor mass from a central chondroma of the upper end of the humerus, and (B) (No. 25766) a similar tumor mass with cystic changes associated with an exostosis in the lower end of the femur These lesions illustrate the prognostic paradox in benign chondromas. The chondromas in the large bones, although typically benign under the microscope, have a decided tendency to recur and undergo malignant change whereas chondromyxomas of the small bones, although resembling a malignant condition under the microscope are clinically benign.

tumor with deep red or black. However these growths are not vascular and the vessels described in the literature particu larly under the old terminology of angio-chondroma, are to be found in the adjacent soft parts and not in the tumor proper

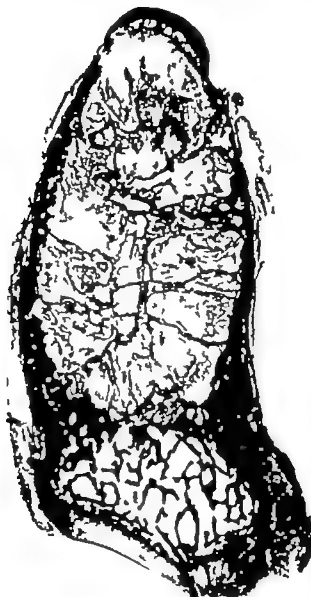


FIG. 51 (No. 33071) Low magnification of a central chondroma occurring in the terminal phalanx of a toe. The lobulated tumor mass is encapsulated by a thin shell of bone and is dis tinctly a benign lesion

In the small bones the structure of the chondroma is fairly characteristic. In most instances the cortical bone is intact (Fig 51) and portions of the cancellous bone remain in one or more areas, either forming the boundary of the tumor or project ing into it as the remains of the original medullary structure. Within such bony confines the gelatinous mass infiltrates everywhere as if it had been poured into a mold and left there to congeal and harden. Within the congealed substance a few gritty areas of calcification may be felt.

About the ribs or spine these growths

are firm, nodular masses which become cystic when attaining to large size. In the rare instances in which these tumors involve a long bone they show greater proliferative powers, and the original mass is reduplicated by similar clusters of lobules. Some of these reduplicated masses may be uniformly gelatinous others are cystic and exude fluid from their smaller pockets. the ribs and spine the hyaline substance is much increased the lobules are larger with fewer strands of connective tissue and the cartilage cells are sparse This type of chondroma resembles in its structure normal joint cartilage and in all probability some of these tumors are hypertrophied and distorted masses from the costochondral junction or vertebral disks.



FIG. 52. (No. 46936) Multiple central chondromas in the humerus and *in the small bones of the hand in a child of nine years.*

These larger tumors of the benign chondroma class are difficult to distinguish in the gross from chondromyxosarcomas, and because of their clinical behavior must be looked on as potentially malignant.

MICROSCOPIC FEATURES

The bulk of the benign chondroma is composed of fairly normal adult cartilage. Under the microscope, this chondral substance shows a matrix of hyaline material *divided into lobules* by acellular strands of eosin-staining connective tissue The cartilage cells lie in pairs or tetrads, in small lacunae, and the nuclei, which readily undergo pyknosis, are surrounded by a generous amount of eosin staining cytoplasm.

Variations of this typical structure depend on the location of the tumor About

In the rare instances of large chondromas in the long bones, necrosis and spotty calcification in the cartilage may be found. Connective-tissue cells are more frequent in the strands which mark off the lobules, and occasional islands of hyaline material in which fetal instead of adult cartilage cells are found are more likely to be seen (Fig. 53)

In the small bones, the microscopic picture is changed by the manner in which the capsule infiltrates from the margin. Here there is much cellular connective tissue and fetal cartilage intermingled to form myxomatous material. The connective tissue at *the margin of these tumors*, which gives rise to such myxomatous areas, shows definite ossification with the formation of islands of new bone This transition from cel

lular connective tissue to myxoma to carti lage with a parallel production of new bone is more typical of chondromyxosarcoma. In fact, if it were not for the location of these tumors in the small bones and their encap- benign, while the chondromas in the larger (sternum, ribs, long bones, etc.) are potentially malignant despite a more benign histologic appearance.

When a large group of tumors of the be-

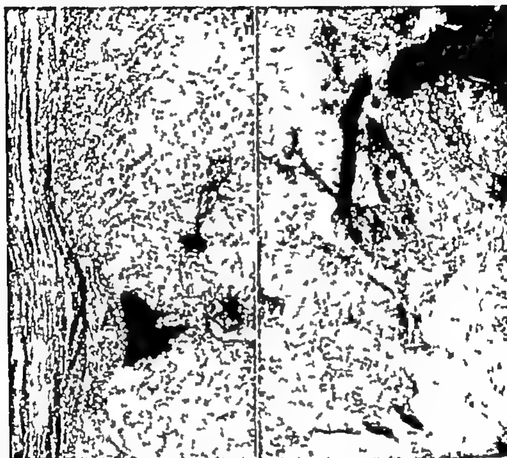


FIG. 53 (No. 38666) Photomicrograph of a cellular area at the margin of a chondroma of a large bone. Numerous spindle cells are present in the connective tissue, and many of the cartilage cells are of the fetal type. An area of spotty calcification is seen. This lesion was in a white woman, aged 37 who had two unsuccessful curettings followed by amputation. The patient is living six years after the first operation. This picture demonstrates the border line type of chondroma in which the exact onset or presence of malignant transformation cannot be determined. Clinically the lesion has been tabulated with chondromyxosarcoma arising secondarily in a benign chondroma.

sulation, the diagnosis of benign chondroma or benign chondromyxoma from a microscopic standpoint would have to be changed in some instances to that of sarcoma (Fig. 54) But in this respect the microscopic picture in these cartilaginous growths is misleading, since the tumors of this type in the small bones of the hands and feet are on the basis of clinical evidence uniformly

nign chondroma class is reviewed microscopically in connection with the sections of many cases of exostosis and also many cases of chondromyxosarcoma, it can be seen that these tumors as a group represent a borderline or transition between the osteochondromas, on the one hand, and the chondromyxosarcomas, on the other

All of these tumors show the same tran-

sition from cellular connective tissue to myxoma with fetal cartilage to adult cartilage with a parallel formation of new bone from connective tissue. In benign osteochondromas, the bone formation predominates, the cartilage is adult cartilage, and strands of active connective tissue and myxoma can be located only as insignificant remnants in the capsule of the tumor. In the benign chondromas, adult cartilage and not bone predominates. In the strands of connective tissue which divide the chondroma into lobules, myxoma and fetal cartilage are nearly always absent, but

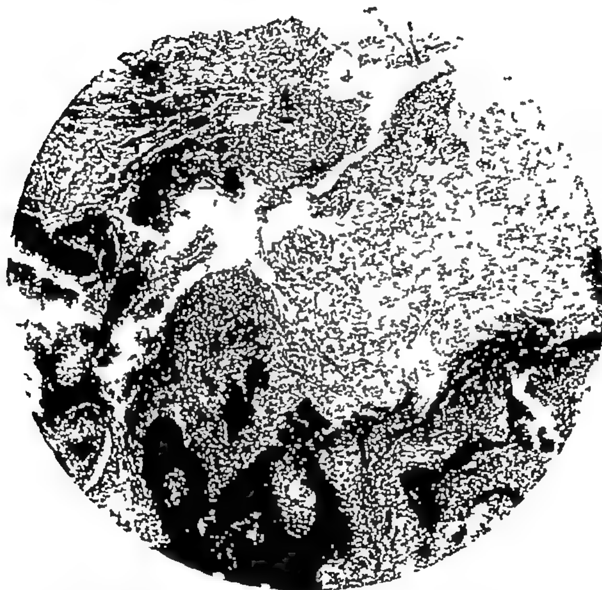


FIG. 54. (No. 23886) Photomicrograph of a central chondromyxoma of the small bones showing the more cellular areas which are responsible for the origin of the tumor. Dense strands of connective tissue can be seen giving rise to fetal and adult cartilage cells. Cartilage is *undergoing calcification* at one point.

in the strands of connective tissue which form the capsule this tissue is easily found. Particularly in the small bones is fetal cartilage a common occurrence, and myxomatous areas along with new bone f
are the *rule* in the margin of

growths. In chondromyxosarcoma, the cellular strands of connective tissue giving rise to myxoma with fetal cartilage infiltrate everywhere and islands of abortive cartilage with malignant nuclei of the vesicular type are replaced at intervals by areas of new bone formation

A graded series of histologic changes in these tumors can thus be traced, the amount and degree of cellular activity in the primitive connective tissue which is the mother substance of these growths, indicating in a general way the degree of the malignancy

HISTOGENESIS

Most of the chondromas and chondromyxomas represent histogenetically supernumerary joint cartilages. In the regions in which they predominate—the hands and feet, the spine ribs and sternum—there are far more joints and articular surfaces than elsewhere in the body Embryologically these joints are laid down by strands of primitive precartilaginous connective tissue which cut across the axis of the future bones at right angles (Fig 55) These precartilaginous strands are the same type of primitive connective tissue that forms the osseous ends of tendons and gives rise



FIG. 55 Photomicrograph showing the development of joint cavities in a human embryo 14 cm in length. At (A) the dense strands of embryonic connective tissue are cutting across the axis of the bone (which is preformed in cartilage) at the site of the future joint cavity At (B) this dense connective tissue is undergoing mucoid regression to form the joint cavity and the capillaries of the future synovial membrane are forming

to the abnormalities of exostoses and osteochondromas. This accounts for the similarity histologically between the chondromas and the exostoses. In forming the joints, this precartilaginous tissue normally undergoes mucoid regressive changes to form the synovial lined joint cavities. However aberrant persisting strands which do not thus regress perhaps are responsible at a later date for the origin of cartilaginous islands in the bone which form the chondromas and chondromyxomas. It is for this reason that the chondromas are found most frequently in a central location in bones in

the regions of the body where there are the greatest number of joints.

The persistence of such precartilaginous tissue about the joints, particularly at the point of reflexion of the joint capsule, may be demonstrated in normal adults (Figs. 23 and 24) Neoplastic tendencies in such tissue are shown in cases of osteochondromatosis of the knee joint (Fig 33) and the potentialities for continued growth are indicated in the chondro-osseous nodules formed in these regions in chronic infectious arthritis. The most conclusive evidence, however is the appearance in these chondromatous tumors of so-called pure myxoma tissue, which is a histologic duplication of the regressive mucoid changes observed in the embryo during the formation of the joint cavities. This myxomatous character is particularly prominent in the chondromas of the small bones and in those chondromatous lesions of the large bones undergoing secondary malignant change (Figs. 57 103)

From a practical point of view it is of importance to understand, if possible, why the chondromas should present a more cellular and myxomatous appearance when they occur in the small bones and yet remain in this location so uniformly benign. Also why on the other hand, should they be more predominantly cartilaginous when occurring in the long bones and yet more prone to malignant change? The explanation is to be found in the capsular changes. In the small bones, the cartilaginous center of the tumor never extends far from the influence of the cortical and periosteal margin of the growth, owing to the limitations of space. Thus the myxomatous strands characteristic of the margin of the chondromas are always readily visible among the cartilaginous areas. At the same time, normal periosteum with its subperiosteal osteogenic layers is capable of reacting to the tumor and laying down a protective shell of new bone (Fig. 51) the reactive changes giving to the tumor its cellular appearance.

In the large bones, the conditions are reversed. The more central lobules of cartilage grow and reduplicate at some distance from the periosteal and capsular margin of the tumor Cellular connective-tissue strands and reactive new bone are therefore less likely to find their way into the chondral substance of the tumor Hence these tumors are more prone to resemble normal adult cartilages. The tendency for malignant change in the precartilaginous tissue associated with large chondromas cannot be explained by the facts at our disposal.

PROGNOSIS AND TREATMENT

When these benign cartilaginous tumors are quiescent and give mild or no symptoms, they are best let alone and kept under observation by repeated roentgen examination. If because of their position they are frequently subjected to trauma, resulting in soreness and discomfort to the patient, their complete surgical removal should be undertaken if this is feasible and the tumor is not too large. In the phalanges the lesion is usually small enough to permit preservation of the continuity of the bone after thorough curetting followed by cauterization. The ease with which this tumor is transplanted should be kept in mind and biopsy should be avoided unless complete removal of the tumor follows forthwith.

Recurrence is not frequent following operation on chondromas in the small bones. Approximately one third of the cases in this series were treated by primary amputation or radical resection, and in all such cases a permanent cure was effected. When curettement is followed by adequate cauterization, either thermal or chemical with 50 per cent zinc chloride, permanent cures have been established in such lesions occurring in the bones of the hand or foot.

In the chondromas occurring in the large bones, recurrences have followed operation in approximately 25 per cent of the cases. In some of these instances the growth returned after repeated partial excisions when



FIG. 56 Benign chondroma of the sternum. This lesion was resected and a tantalum plate was inserted as an artificial manubrium

the neoplasms, because of location, could not be completely removed. It is important to record here that patients followed from five to ten years after the first observation have remained well without treatment, although in some instances such as the case shown in Figure 48 there has been a gradual increase in the size of the tumor and ultimately death from compression.

When a previously quiescent tumor shows sudden signs of increased growth, with an exacerbation of symptoms, immediate and complete removal is indicated, as secondary malignant change is to be expected. In the instances in which the patient has been so unfortunate as to neglect the growth and allow the tumor to become of unusual size, or in which the location about the sternum or spine makes complete removal difficult or dangerous, irradiation therapy may be attempted. While the clinical follow-ups on malignant cases arising from pre-existing benign tumors of this group indicate that these lesions are radioresistant, such therapy is indicated for palliative reasons. Incomplete removal by surgery is often followed by recurrence and is to be avoided. If biopsy has been performed, radical resection should follow. If this is not feasible because of location, the excision should be followed by cauterization and irradiation.

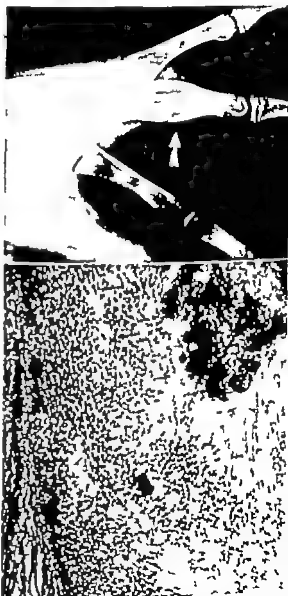


FIG. 57 Roentgenogram and photomicrograph of a central chondroma of the phalanx successfully treated by curettage and cauterization with 50 per cent zinc chloride followed by alcohol.

In deciding whether a particular lesion in this group is to be treated from the benign or malignant standpoint, the location and not the pathologic changes must be given primary consideration. Chondromas occurring in the small bones of the hand or foot (the os calcis and astragulus excepted) regardless of their pathologic appearance, may be looked on as being curable by thorough extirpation (curetting and cauterization) True chondromas of large size occurring about the sternum, spine pelvis or in the long bones, regardless of their microscopic appearance must be looked on as potentially malignant, and their complete surgical removal, if feasible, should be attempted. Resection of the manubrium may be successfully performed for chondroma (Fig 56)

SUMMARY

A common type of cartilaginous tumor often classified with the benign exostosis is the benign chondroma. These tumors differ histologically from the osteochondromas in that the osseous material typically present in the latter is absent or sparse in these cartilaginous lesions and their location in the skeleton is most frequently central instead of periosteal. The chondroma is a benign lesion occurring in the small bones of the hands, feet or spine and about the ribs and sternum in patients between the ages of 20 and 30 years. In the phalanges of the hand, where this tumor is most frequently located, the growth produces a central rarefaction, with stippling or striations in an expanded or cystic area within a shell of cortical bone. Contrary to the usual belief the central chondroma is rarely multiple and rarely affects the long bones.

Clinically the symptoms are mild and protracted, extending on the average over five years and producing recurrent soreness in a swelling of stationary or slowly increasing size. Cures may be achieved by complete excision or curettement followed by cauterization, but because histologically there are strands of early connective tissue and myxoma associated with the adult cartilage which makes up the bulk of this tumor these lesions are apt to recur if incompletely excised. In the prognosis of these tumors, it is a striking paradox that the more cellular chondral lesions in the small bones associated with fetal cartilage and myxoma are uniformly benign, whereas the less cellular tumors of larger size occurring in the sternum and long bones, although composed of benign adult cartilage, must be looked upon clinically as potentially malignant.

Histogenetically these tumors probably represent supernumerary joint cartilages, derived from a prechondral connective tissue which normally forms the joints of the body This explains their occurrence in the small bones of the hands and feet and about the sternum and the spine where there are a great many articular surfaces. In these regions aberrant strands of primitive connective tissue traverse the axis of the future bone at right angles and become enclosed as development progresses, gradually giving rise to central chondromas.

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5

Forms of Osteogenic Sarcoma—Primary Chondrosarcoma

ORIENTATION

Osteogenic sarcoma was originally defined as a tumor either produced by bone or producing bone. It is a malignant tumor derived from skeletogenic mesenchyme which repeats in its growth one or more phases of bone development. There are several subvarieties, but from the practical viewpoint they have much in common They occur predominantly in adolescence or early adult life. They involve the long bones more frequently than the flat bones. Their favorite sites are the lower femur and the upper tibia. They are radioresistant unless the tissue is highly vascular hence radical surgery is the treatment of choice In the roentgenogram they are unconfined by the anatomic zones of bone structure. The tumor tends to involve the cancellous structures, the cortex, the subperiosteum and the periosteum, and to escape into the soft parts. In traversing these zones, it results in periosteal lifting with the production of new bone All osteogenic sarcomas therefore, tend to destroy bone and also to produce bone either through their own cycle of development or by their effect on preexisting bony structures. All osteogenic sarcomas tend to metastasize by the blood stream to the lungs and terminate fatally unless treated radically at an early date.

There are two main groups of osteogenic sarcoma those which produce cartilage as the end-point of their differentiation, and those which produce osteoid or osseous material. The majority of cartilaginous tumors arise from central islands of cartilage within the cancellous spaces or from benign chondromas or osteochondromas. A smaller percentage of chondral sarcomas arise periosteally from persisting perichondrium. Some of the chondrosarcomas arise from the cartilage of the epiphyseal plate and are termed chondroblastomas.

As stated, most of the malignant cartilaginous growths are secondary to rests or some form of benign cartilage-containing tumor They grow slowly tend to recur and transplant after local excision and to metastasize from three to ten years after the initial operation, if not cured by radical surgery They contain pockets of jellylike material among the firmer hyaline tissue The percentage of late cures following incomplete operations is high and has misled some observers into thinking that early inadequate treatment immunizes against the tumor The periosteal primary chondrosarcomas are highly malignant growths and they tend to merge in their characteristics with the periosteal osteoblastic sarcomas described below

The chondroblastomas arise from the

epiphyseal cartilaginous plate and may be benign or malignant. They are rare and have caused much discussion since we called attention to them in the first edition of this book.

The osteoblastic sarcomas may be subdivided into those arising from the periosteum and those arising from the endosteum. The periosteal growths may be predominantly osteoblastic and sclerosing, or may be more malignant growths with cartilage, and overlap with the primary chondrosarcomas. The endosteal osteogenic sarcomas may be predominantly bone-forming and sclerosing, like those in the periosteum, but more often they are composed of vascular fibrous tissue which only partly ossifies and hence they are osteolytic in character. It will be remembered that the endosteum has two functions (1) the elaboration of a vascular connective tissue which resorbs calcified cartilage (this phase of its development we have termed angiospongiosa) and (2) the same tissue later forms cancellous from fibrous tissue, a process which we have termed fibrostosis. The majority of endosteal tumors are of the angiospongy variety and clinically are central osteolytic sarcomas. Some of them exhibit mainly fibrostosis and are sclerosing tumors. In any event, the endosteal tumors are characterized by an absence of cartilage. We have chosen arbitrarily to separate the sclerosing from the osteolytic tumors because of their difference in clinical and pathologic appearance and because the osteolytic tumors are moderately radiosensitive.

The sclerosing tumors are practically confined to adolescents. They produce new bone, which invades and clouds the cancellous structures in the roentgenogram and projects into the periosteal zone as a characteristic sunburst. They are radioresistant, but nearly one-third of the cases can be cured by early amputation.

The osteolytic sarcomas are highly vascular destructive lesions which show only minimal amounts of osteoid tissue or none at all on microscopic examination. They arise from endosteum and are confined, for the most part, to the cancellous structures. They erode the cortex and lift the periosteum, but produce minimal amounts of periosteal new bone. They have a wide age distribution from childhood to late adult life. These tumors are moderately radiosensitive, but are not cured by such treatment, and early amputation is the treatment of choice.

TABLE 8. CLASSIFICATION OF OSTEOGENIC SARCOMA

	Chondrosarcoma	Osteoblastic Sarcoma
Origin	Persisting perichondrium Central cartilaginous rests Osteochondroma and chondroma (epiphyseal plate)	Endosteum Periosteum
Types	Primary periosteal chondrosarcoma Secondary chondrosarcoma Malignant chondroblastoma	Sclerosing sarcoma Osteolytic sarcoma

While many chondrosarcomas are secondary to benign cartilaginous tumors, a smaller percentage of osteoblastic sarcomas complicate pre-existing benign lesions of bone. The osteolytic forms may develop in irradiated giant-cell tumors, or in a bone affected by Paget's osteitis deformans or by fibrous dysplasia. Osteogenic sarcoma complicating myositis ossificans has been reported by several observers. We have observed it in acromegaly of the jaw in fibrous dysplasia and once in the callus of an ununited fracture. The osteoblastic forms of sarcoma have been produced in experimental animals by injecting radioactive material, intramuscularly or by the implantation of radium needles next to bone (Lacassagne and Brunschwig). Pybus and Miller have described a strain of mice with spontaneous osteogenic sarcoma. Martland described sarcoma of bone following ra

dium poisoning in girls engaged in painting the luminous dials of watches.

In the discussion of the several forms of osteogenic sarcoma, in the chapters which follow it is pointed out that the five-year survivals are highest with treat ment by radical surgery These survivals vary from 10 to 35 per cent. They are low est in the undifferentiated periosteal chon drosarcomas and in endosteal osteolytic sarcomas. They are highest in the chondro-sarcomas, secondary to benign cartilaginous growths, and in sclerosing sarcoma. As a rule, the cases of sclerosing osteogenic sar coma which remain well five years following amputation or radical resection represent permanent cures. In secondary chondro-sarcoma, however late recurrence and metastasis may take place from seven to ten years after the primary treatment.

Since the first edition of this work, numer ous contributions to the American literature have confirmed the curability of sarcomas of bone. Reports based on a significant series of followed cases have been pub lished by Simmons, by Coley and Pool, by Ferguson, by Badgley and Batts, and by MacDonald and Budd. Badgley and Batts followed 80 cases, of which 17 were living at the time of the report. There were 15 five-year survivals or 19 per cent. Older patients, and those with a longer duration of symptoms, had a better prognosis. Mac-Donald and Budd, in 1943, reviewed 115



FIG. 58 (No 42358) Roentgenogram and gross specimen of a primary chondromyxosarcoma. The patient was a white boy aged 18, with an onset of symptoms one month previously of pain and tumor in the medial aspect of the lower end of the femur The lesion was explored, and amputation done. The patient died nine months later The roentgenogram shows a translucent periosteal shadow above the internal condyle of the femur with definite periosteal lipping above and radiating spicules (probably calcified) next to the bone. The gross specimen shows more definitely the actual size and location of the tumor mass emphasizing the translucent character in the roent genogram of most of the tumor substance.

five-year cures from the Bone Registry Their five-year survivals averaged 11.8 per cent for osteosarcoma and 47.5 per cent for chondrosarcoma.

PRIMARY CHONDROSARCOMA

The largest group of tumors among osteogenic sarcomas contain cartilage in association with a type of myxomatous connective tissue, indicating an origin analogous to the benign exostoses and chondromas (Geschickter*) As in the analysis of the benign lesions (in the foregoing chapters) this form of connective tissue can be traced to a survival at points in the skeleton of primitive perichondrium and periarticular strands of precartilaginous tissue.

The relationship of these chondral forms of osteogenic sarcoma to the benign tumors of the fibrocartilaginous group is, therefore, an intimate one, and the origin of these various neoplasms is so nearly identical that it is often impossible, even with all the data at hand, to predict whether the outcome of the growth will be benign or malignant.

However among these lesions there is a primary form of chondromyxosarcoma which shows from the start its sarcomatous nature. It is a very malignant tumor arising as a rule periosteally which does not at the onset involve either the cortex or the medullary cavity of the bone (Figs. 58, 59 and 60) In the roentgenogram it is characterized by its translucent and nearly invisible periosteal shadow The distinguishing microscopic composition shows loose myxomatous connective tissue merging into zones of fetal cartilage and chondral areas with an abundant hyaline matrix, fringed by osseous tissue. This indicates its proliferative powers, yet identifies this sarcoma with the more benign tumors of the fibrocartilaginous group

Clinical Features

The clinical features of primary chondrosarcoma reflect in part the primitive histogenesis of this neoplasm. The frequency with which Negroes are affected (approximately 15 per cent) is unusual among the osteogenic sarcomas as a group and suggests a lower evolutionary form of osteogenesis for this tumor The extremely malignant clinical course also implies a primitive tissue of origin. These clinical aspects of this neoplasm, the tendency for the tumor to be related to periarticular structures and the rapid clinical course with its usually fatal outcome may be singled out as fundamental characteristics of the growth.



Fig. 59 (No. 37930) The translucent periosteal shadow typical of primary chondrosarcoma is shown in the lower end of the femur at the site of the adductor tubercle

These tumors occur in patients under 30 sarcoma of this form appearing most frequently in patients from 14 to 21 years, in the postadolescent period (Tables 9 and 10, Chart 4) The youngest patient in this

* Geschickter C. F.: Osteogenic sarcoma, Arch. Surg., 24 602, 798, 1932.

series affected with a primary chondrosar coma was ▮ years old, the oldest 57

The favorite sites for these lesions are about the knee and at the shoulder and occasionally involved. In the upper end of the tibia, the insertion of the quadriceps tendon at the tibial tuberosity is most fre quently affected.



FIG 60 (No 37930) Photomicrograph showing pleomorphic cartilage cells enclosed in lobules that simulate a benign chondroma. The strands of embryonic connective tissue and calcification bear evidence of the malignant nature of the tumor

pelvic girdles (Fig 61) The majority are about the knee in the lower end of the femur or upper end of the tibia. In the lower end of the femur the line of insertion of the adductor magnus along the linea aspera and at the adductor tubercle on the medial condyle are favorite sites. The point of origin of the lateral head of the gastrocnemius at the external femoral condyle is

The distribution of these lesions shows a relationship to points of muscular attachment and to articular regions where cartilage formation persists throughout life. These sites of muscle attachment are, as has been seen, those of the long muscles exerting a maximal traction, such as the quadriceps femoris, the adductor magnus and the gastrocnemius. As in the exostoses, the

points of origin for this type of tumor show an anatomic peculiarity in the periosteum Here the normal fibrous layers are interrupted to allow osseous fusion with the end of a tendon, and at the point of fusion, precartilaginous tissue, from which such structures as the adductor tubercle or the tuberosity of the tibia are formed, persists both beneath the periosteum and within the substance of the tendon.

The symptoms in this primary form of chondrosarcoma have existed for about five months before examination and begin with a complaint of pain which may or may not follow a relatively mild form of trauma. The pain becomes rapidly more constant and severe and soon interferes with the function of the part. Since the region of the knee is usually involved, the stiffness of this joint, with the assumption of a position of partial flexion is common. Weight-bearing in the affected leg soon becomes painful, and limping is followed by the use of crutches, full relief soon being impossible even when the part is put at complete rest.

Examination reveals swelling in the region of the flexed joint and a tumor with a rubbery consistency that is larger to palpation than the roentgenograms would seem to indicate Pathologic fracture is exceedingly rare because of the acute course and the periosteal nature of the lesion. Among the constitutional manifestations of primary chondrosarcomas, fever leukocytosis and an enlargement of the regional lymph nodes are occasionally observed. The glandular enlargement is noted only in association with fever and, to our knowledge, metastases to these glands have not been demonstrated by histologic examination, although such secondary growths in other forms of osteogenic sarcoma have been recorded These systemic reactions as well as a secondary anemia are late manifestations of

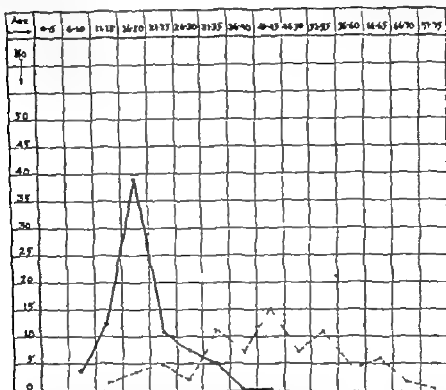


CHART 4 Chart showing age incidence among cases of primary chondromyxosarcoma. The solid line indicates the curve in 79 cases of primary chondromyxosarcoma, the broken line in 75 cases of secondary chondromyxosarcoma.

TABLE 9 PRIMARY CHONDROSARCOMA

Pathologic No	Race	Sex	Age	Location	Duration	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
66337		M		Region of lung and trachea	1 mo	Weakness, temperature	Right lung congested, tumor pushing heart to right side			Lost
62762	W	F	15	Sternum		Pain, tumor	Bone radiating spicules on under surface of gladiolus	Excision 1945	Degenerating cartilaginous masses	Dead 1 yr
62716	\	M	16	Right femur	10 da.	Pain, tumor	Periosteal mass		Lobules of hyaline cartilage	Dead 1 yr
62426		M		Sternum	3–4 mos.	Loss of weight	Rarefaction and erosion of manubrium		Chondrosarcoma	Well 5 yr
62214	W	F	12	Tibia	12 mos.	Pain swelling	Irregularity of epiphyseal line, upper tibia	Exploration		Dead 1 yr
62006	W	M	15	Clavicle	12 mos.	Tenderness		Surgery	Malignant precartilaginous connective tissue with areas of fetal cartilage	Well 7 yr
61828	W	M	15	Femur left	6 mos.	Mass, left knee	Sclerosis of femoral shaft, splitting of cortex, proliferation of periosteal new bone chest negative	Amputation		Dead 3 yr
61610	W	F	13	Tibia, right		Pain, tumor	Destruction of cortex right tibia, periosteal new bone and semi-translucent mass projecting into soft parts	Biopsy	Malignant connective tissue and masses of hyaline cartilage	Well 8 yr

61570	W	M	19	Fibula mid portion	12 mos.	None			Interlacing strands of spindle cells, embedded in translucent matrix malignant and precartilaginous cells and fetal cartilage	Lost
60090	W	M	20	Tibia	12 mos.		Rarefaction on either side of epiphyseal line, head of right humerus			
60230	W	F	26	Tibia, right	13 mos.	Recurrent swelling, pain	Rarefaction base of medial condyle, erosion in tibia	Amputation	Fetal cartilage degenerating hyaline cartilage and small foci of precartilaginous connective tissue	Well 9 yr
60216	W	M	10	Hip, right		Pain swelling	Negative	Radical excision	Fetal and adult cartilage and proliferating precartilaginous connective tissue	Lost
58250	W	F	25	Tibia, upper end	21 mos.			Operation curettage and graft amputation	Cartilage cells new bone formation cellular connective tissue	Well 11 yr
58172	W	F	13	Scapula	14 mos.	Limitation of motion	Mass over scapula destroying bone		Fibrospindle cell tissue with hyperchromatic nuclei	
57712	W	M	14	Fibula	16 mos.		Periosteal shadow upper end of fibula calcareous markings radiating at right angles to shaft	Curettage	Strands of precartilaginous connective tissue and numerous fetal cartilage cells	Dead 2½ yr

TABLE 9 PRIMARY CHONDROSARCOMA (*Continued*)

Pathologic No	Race	Sex	Age	Location	Duration	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
57282	W	F	44	Femur	9 mos.		Honeycombed rarefaction underlying periosteal reaction	Irradiation	Proliferating cartilage adult & fetal	Hopeless recurrence in 4 yr
50006	W	M	67	Ischium right	5 mos.		Irregular areas of calcification invasion of soft parts		Proliferating cartilage adult & fetal	
51932	W	M	41	Scapula	18 yr			Resected, 1935	Proliferating cartilage adult & fetal	Dead 2 yr
55708	W	F	11	Tibia, right	3 mos.			Amputation 1935	Proliferating cartilage adult & fetal	Well 3 yr
52046	W	M	20	Tibia	3 mos.			Amputation 1934	Proliferating cartilage adult & fetal	Dead 9 mos.
52574	W	M	18	Femur left			None	Biopsy Jan 1934	Proliferating cartilage adult & fetal	
52516	W	M	27	Vertebra	1 mo		None	Laminectomy Aug., 1933	Proliferating cartilage adult & fetal	Dead 1 yr
52172	W	F	26	Radius	12 mos.			Amputation 1933	Proliferating cartilage, adult & fetal	Dead 2 yr
52104	W	M	12	Humerus, upper half	4 mos.		Rarefaction pathologic fracture, periosteal reaction	Irradiation 1932	Proliferating cartilage adult & fetal	Dead 2 yr
51068	W	F	44	Femur	Recurrence 70 mos.		Periosteal reaction, central erosion	Primary excision 1927 recurrence and excision 1933	Proliferating cartilage adult & fetal	Dead 3 yr
51852	C	F	40	Ulna	12 mos.		Central cystic lesion	Local excision Aug. 1933	Proliferating cartilage adult & fetal	Dead 3 yr
51450	W	M	53	Humerus	6 mos			Irradiation, 1933	Proliferating cartilage adult & fetal	Dead 6 mos.
51324		F	30	Fibula	10 yr		Periosteal involvement	Resected 1933	Proliferating cartilage adult & fetal	Well 5 yr
51296	W	M	20	Femur	2 mos.			Irradiation, 1933	Proliferating cartilage adult & fetal	Dead 1 yr

40831	W	M	18	Tibia	3 mos.		Central rarefied lesion with slight stippling at margin	Roentgen therapy Feb., 1933 amputation 4-28-33		Well 15 yr
10208	W	M	32	Tibia	21 mos.	None	Multiple spurs overgrown by calcified periosteal tumor	Local operation		Well 1 mo
49208	W	M	15	Os calcis				Biopsy Oct., 1932 Biopsy Nov 1932		
48031	W	M	15	Ilium	24 mos.		Periosteal reaction central erosion	Biopsy 1930		Dead 1 yr
48750	W	F	28	Pelvis	5 mos.			Irradiation, 1932		Dead 1 yr
48578	W	M	50	Femur	9 mos.		Punched-out appearance periosteal reaction	Biopsy 1931		Dead 6 yr
40808	W	M	16	Humerus	6 mos.			Amputation, 1931		Well 6 yr
47053	W	M	26	Femur	4 yr			Amputation, 1932		Dead 9 mos.
45771	W	F	25	Femur	4 yr			Irradiation 1931		Dead 6 mos.
45658	W	F	13	Vertebra	9 mos.			Excision, 1931		Dead 9 mos.
41456	W	F	20	Tibia	12 mos.			Excision, 1931		Dead 6 mos.

TABLE 10. PRIMARY CHONDROMYXOSARCOMA

Pathologic No.	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
43830	W	M	34	Femur, lower	10	Pain; swelling	Translucent periosteal shadow	Amputation	Chondromyxosarcoma	Well 2 mos.
43306	W	M	57	Humerus	13			Amputation 1930		Dead 6 y
43610	W	F	18	Femur lower	2	Pain swelling	Translucent periosteal shadow	Irradiation, amputation		Well 8 yr
43724	W	F	24	Femur	13			Amputation 1930		Dead 2 yr
42994	W	F	10	Femur lower	7	Pain; swelling	Periosteal shadow bone destruction	Curettement; amputation	Chondromyxosarcoma	Dead 1 yr
42984	W	F	24	Humerus, right upper	2	Pain; swelling	Periosteal shadow bone destruction	Biopsy; irradiation, amputation	Chondromyxosarcoma	Dead 5 mos. later
42358	W	M	18	Femur lower medial	1	Tumor; pain	Translucent periosteal shadow; slight bone destruction beneath	Exploration amputation	Chondromyxosarcoma *	Dead 9 mos. later †
42356	W	M	19	Femur lower	2	Trauma	Translucent periosteal shadow; some radiating new bone	Exploration; amputation	Chondromyxosarcoma	Discharged well
42359	W	M	20	Tibia, lower	5	Trauma; pain; tumor	Translucent periosteal shadow at tuberosity	Amputation	Chondromyxosarcoma	Discharged well
42350	W	M	17	Femur lower external condyle	5	Pain; tumor	Translucent periosteal shadow slight bone destruction beneath	Amputation	Chondromyxosarcoma	Discharged well
42348	W	F	20	Tibia, upper	9	Pain; tumor	Translucent periosteal shadow; some radiating new bone	Exploration; excision; radium	Chondromyxosarcoma	Living 20 mos. after first operation
42346	W	F	13	Tibia, shaft	8	Trauma, tumor	Translucent periosteal shadow; some radiating new bone	Amputation	Chondromyxosarcoma	Well 3 yr
42344	W	F	13	Femur lower	3	Tumor	Translucent periosteal shadow some radiating new bone	Erysipelas and prodigiosus toxins (Coley's)		Dead 7 mos. later
42343	W	M	18	Femur upper	5	Tumor pain	Translucent periosteal shadow	Exploration, amputation	Chondromyxosarcoma	Dead 11 mos. later
42325	W	M	27	Femur, upper middle	3	Pain, 3 months; swelling, 1 week	Translucent periosteal mass; right angle new bone	Roentgen therapy		Dead 1 yr later
42175	W	M	18	Tibia, upper	5	Trauma, tumor	Translucent periosteal shadow at tuberosity	Irradiation		Dead 5 y
41842	W	F	11	Astragalus, left	1½	Pain; swelling	Periosteal roughening	Curetted; amputation advised but not done	Chondromyxosarcoma	Dead 2 yr later
41[illegible]	W	M	16	Humerus, upper left		Pain; tumor	Translucent periosteal shadow; radiating bone	Irradiation		Dead 6 mos. later
41503	W	M	44	Jaw left, lower	4	Pain, teeth extracted; tumor	Area of bone destruction	Radium; excision	Chondromyxosarcoma	Living 6 mos.

41419	W	F	16	Fibula, right, upper	3½	Tumor	Destruction with periosteal roughening	Amputation	Chondromyxosarcoma	Dead 6 mos. later
41122	W	F	17	Tibia, upper	4½	Pain; swelling	Periosteal bone destruction and bone formation	Amputation	Chondromyxosarcoma	Well 9 yr later
41093	W	M	6	Femur, upper		Tumor	Translucent periosteal shadow	Roentgen therapy	Chondromyxosarcoma	Well 10 mos. later
41016	W	?	15	Femur, lower	4	Pain; tumor; limp	Translucent periosteal shadow; bone destruction beneath	Amputation	Chondromyxosarcoma	Dead 3 yr later. Metastasis to lung
41008	W	F	18	Femur, lower		Tumor	Translucent periosteal shadow; bone destruction beneath	Curetted; amputation later	Chondromyxosarcoma	Dead 6 mos. after amputation
40719	W	M	33	Tibia, head		Tumor		Amputation	Chondromyxosarcoma	Dead 8 mos. later metastasis to chest and skull
40699	W	M	30	Humerus	1	Pain; stiffness	Translucent periosteal shadow; slight bone destruction beneath	Resection	Chondromyxosarcoma	Dead—recurrence 3 yr later
40364	W	M	13	Tibia, upper	3	Pain; tumor		Amputation	Chondromyxosarcoma	Dead 1 yr later
40191	W	M	22	Second rib and clavicle	6	Pain; tumor		Erysipelas and prodigiosus toxins (Coley's)‡		Dead 4 mos. later
40181	W	M	12	Femur, lower		Pain	Translucent periosteal shadow; expansion and destruction	Roentgen therapy		Well 1 yr
40330	W	F	16	Eleventh rib	3	Tumor	Expansion and destruction	Roentgen therapy and radium		
40318	W	F	19	Scapula	7			Excision 1922		Dead 4 yr
39794	W	M	18	Femur, lower	½	Tumor; pain	Translucent periosteal shadow; radiating new bone	Amputation	Chondromyxosarcoma	Dead 11 mos. later
39180	W	M	12	Humerus, shaft	12	Tumor	Translucent periosteal shadow	Irradiation		Well 8 yr later
39140	W	M	9	Femur, lower	1	Pain; tumor		Exploration	Chondromyxosarcoma	Well 14 yr later
38514	W	M	18	Femur, lower	6	Tumor	Periosteal translucent shadow	Excision	Chondromyxosarcoma	Recurred 6 mos. later
38820	W	F	16	Tibia, upper	6	Trauma; pain; tumor	Periosteal translucent shadow	Amputation	Chondromyxosarcoma	Dead 4 yr
38366	W	M		Femur, shaft		Tumor; pain		Amputation	Chondromyxosarcoma	Dead 3 yr later

* The term chondromyxosarcoma indicates a microscopic picture comprising: myxoma, fetal, adult and calcifying cartilage and occasional new bone formation.
† The results given show the duration calculated from the date of treatment. *The duration of symptoms is from the subjective onset.*
‡ Otherwise referred to as toxins.

TABLE 10 PRIMARY CHONDROMYXOSARCOMA (*Continued*)

Pathologic No.	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
38410	W	M	45	Jaw lower	7	Pain abscess	Bone destruction	Drainage and [illegible]	Chondromyxosarcoma	Dead 2 yr later
38214	W	M	37	Humerus	12			Irradiation; biopsy 1926		Dead 4 mos.
37830	W	M	18	Femur lower	3	Trauma; pain	Translucent periosteal shadow	Irradiation, amputation	Chondromyxosarcoma	Dead 1 yr later
37224	W	M	14	Tibia, upper	9	Pain; tumor	Translucent periosteal shadow	Roentgen therapy		Dead
36620	W	M	34	Humerus, shaft		Tumor	Translucent periosteal shadow	Irradiation; amputation		Dead 6 mos. later
36484	W	F	9	Tibia, upper	6	Trauma; pain; limp	Translucent periosteal shadow	Exploration; amputation; toxins	Chondromyxosarcoma	Dead 6 mos. later
36218	W	M	24	Tibia	12			Irradiation; biopsy 1925		Dead 2 yr
35532	W	M	15	Femur lower	3	Pain tumor	Translucent periosteal shadow; radiating new bone	Irradiation; amputation	Chondromyxosarcoma	Dead 18 mos. later
35010	W	M	23	Radius, shaft	3	Pain	Translucent periosteal shadow	Curettement		
34104	W	M	22	Femur	24			Amputation 1922		Dead 7 mos.
34084	W	M	28	Tibia, upper		Pain	Translucent periosteal shadow; bone destruction	Amputation; irradiation		Dead 1 yr later
34036	W	M	17	Humerus, upper	27	Trauma; tumor	Translucent periosteal shadow	Roentgen therapy and serum		Dead 3 yr later
33063	W	M	22	Tibia	12			Amputation 1922		Well 16 yr
33024	W	F	18	Humerus, upper	2	Trauma; pain; tumor	Translucent shadow of soft part	Irradiation		Dead 2 mos. later
32980	W	M	19	Tibia, upper	10	Pain; tumor	Translucent periosteal shadow; radiating new bone	Amputation	Chondromyxosarcoma	Dead 3 yr later
32909	W	M	19	Femur lower	3	Trauma; pain; tumor	Translucent shadow of soft part; bone destruction	Roentgen therapy; toxins; amputation	Chondromyxosarcoma	Well 10 yr later
32346	W	F	16	Tibia, upper	3	Trauma; pain; tumor	Periosteal shadow; bone destruction	Irradiation; exploration	Chondromyxosarcoma	Dead 1 mo. later
32131	C	M	13	Femur lower	3	Pain; swelling	Translucent shadow of soft part	Roentgen therapy		Lost
31940	C	F	25	Femur	8	Tumor	Translucent periosteal shadow; radiating new bone and bone destruction	Amputation	Chondromyxosarcoma	Well 12 years
31322	W	M	14	Tibia, upper	4	Pain; tumor	Translucent periosteal shadow; radiating new bone	Excision, amputation	Chondromyxosarcoma	Dead 2 yr later
30680	W	M	33	Ilium crest and pelvis	4	Pain; tumor	Translucent periosteal shadow; bone destruction beneath	Irradiation; toxins		Dead 1 y later
30478	C	F	33	Tibia, upper	17	Pain; tumor	Translucent periosteal shadow; bone destruction beneath tuberosity	Resection; amputation	Chondromyxosarcoma	Lost

25468	C	M	22	Ulna, shaft	1	Pain; tumor	Translucent periosteal shadow; radiating new bone	Amputation		Well 6 yr after
20871	W	M	19	Femur lower	3	Pain; tumor	Translucent periosteal shadow; bone destruction beneath	Irradiation; amputation	Chondromyxosarcoma	Dead 2 mos. later
28700		F	23	Radius	6	Tumor		Exploration; curettement; roentgen therapy; tumor	Chondromyxosarcoma	Dead
25306	W	F	24	Tibia, upper	6	Tumor; pain	Periosteal translucent shadow	Amputation	Chondromyxosarcoma	Dead 5 yr later
28220	W	M	18	Femur lower	4	Pain; tumor		Amputation	Chondromyxosarcoma	Dead 2 yr later (metastases to liver and intestines)
28267	W	M	18	Femur lower	1	Trauma; tumor	Translucent periosteal shadow	Amputation radium	Chondromyxosarcoma	Dead 3 mos. later (metastases to bone)
27824	W	M	10	Tibia, upper	1	Pain; tumor	Translucent periosteal shadow	Excision	Chondromyxosarcoma	Dead 6 mos later
27085	C	F	18	Femur lower	4	Pain; tumor		Amputation; irradiation	Chondromyxosarcoma	Dead 6 mos later
27451	W	M	20	Femur lower	3	Pain; tumor	Translucent periosteal shadow	Exploration; amputation		Died, second operation
23637	W	M		Femur lower				Excision	Chondromyxosarcoma	
21357	W	M	17	Femur lower	1	Pain	Translucent periosteal shadow; radiating new bone	Amputation	Chondromyxosarcoma	Dead 12 mos. late
20166	W	M	16	Fibula, upper	2	Pain; tumor	Periosteal new bone; bone destruction	Incision; curettement	Chondromyxosarcoma	Dead 3 yr later
19419	C	F	18	Femur lower	3	Pain; swelling	Calcifying periosteal shadow	Amputation	Chondromyxosarcoma	Dead 7 mos. later
17564	C	F	14	Tibia, upper	6	Trauma; tumor		Amputation	Chondromyxosarcoma	Dead 3 yr later
17528	W	M	20	Femur lower	3	Trauma; tumor	Translucent periosteal shadow; radiating new bone	Amputation	Chondromyxosarcoma	Dead
16347	W	F	20	Tibia, upper	2	Pain; tumor	Periosteal new bone; bone destruction	Amputation	Chondromyxosarcoma	Dead 15 mos. later
15638	W	M	21	Humerus	8	Pain; tumor		Amputation	Chondromyxosarcoma	Dead 13 mos. later
15457	W	M	21	Femur, lower	2	Pain; tumor	Periosteal new bone; bone destruction	Amputation	Chondromyxosarcoma	Dead 3 yr later
11670	W	M	17	Tibia, upper	8	Pain; tumor	Translucent periosteal shadow; bone destruction beneath	Amputation	Chondromyxosarcoma	Dead 1 yr later
8066	W	M	17	Sacrum, upper	12	Trauma; tumor; paraplegia		Exploration	Chondromyxosarcoma	Dead 1 yr later
2331	W	M	17	Vertebra, lower lumbar	12	Trauma; pain		Exploration	Chondromyxosarcoma	Dead 1 yr later
1880	W	F	22	Ischium	48	Trauma; pain		Partial excision	Chondromyxosarcoma	Recurrence 7 mos. later dead 1 yr

the disease and should play no part in making the diagnosis

Roentgenographic Features

Three important features are typical of the roentgenogram of primary chondrosar

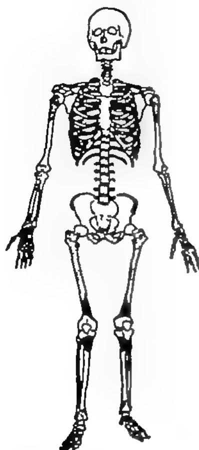


Fig. 61 Incidence of primary chondromyxosarcomas according to skeletal location. The solid black areas indicate the most frequent sites the checked areas, the common sites, and the diagonal lines, the occasional or rare locations.

coma. These are the faintly visible translucent shadow of the soft part next to the bone, the raising of the adjacent periosteum and the frequent absence of cortical or medullary involvement. The entire tumor is outside of the bone proper in early cases, and because its cartilaginous substance casts so little shadow on the film, this may well be considered the invisible tumor of the bone which is in danger of being overlooked or misdiagnosed. When new bone or calcification of tumor origin is present, it is always sparse and has a tendency to take the form of finely radiating lines at right angles to the cortex (Fig. 58) Unlike the sun-ray" or sclerosing type of osteogenic sarcoma, dense shaggy lines of periosteal new bone are lacking This type of sarcoma also differs from the sclerosing form in that it is less likely to involve the marrow cavity When it does so late in the disease, bone destruction is noted in the medulla rather than in areas of increased density as in the sclerosing form (Fig. 64)

This primary form of chondrosarcoma is to be distinguished in the roentgenogram from the benign osteochondromas by its more faintly visible tumor shadow by its indefinite and infiltrating outward margin and also by the failure of the cortex beneath the tumor to form a base or pedicle for the growth as it does in exostoses (Fig 68) When such a chondromyxosarcoma arises as a secondary malignant change in a benign exostosis, this sarcomatous transformation in the benign tumor is evident in the roentgenogram by the blurring and blotting out of the distinguishing lines differentiating cancellous from cortical bone in the base of the exostosis, and the whole tumor soon becomes a stippled and granular mass (Fig 63) These secondary chondrosarcomas are discussed separately in more detail below

The early stage of myositis ossificans may be mimicked (Lewis*) by the delicate lines of ossification in this form of chondrosarcoma, but in the sarcoma the outer border of the tumor never has the definite edge seen in myositis ossificans, and the laminated bony structure paralleling the shaft of the bone is absent. The favorite location of myositis ossificans in the adductor muscles of the thigh and the brachialis anticus of the elbow is not a common site of this form of osteogenic sarcoma, nor is there

* Lewis, D: Myositis ossificans, J.A.M.A. 80: 1281 1923.



FIG. 62. Roentgenograms of primary chondrosarcoma There is erosion of the cancellous bone as well as an overlying periosteal reaction.

the same definite relationship to a trauma preceding the *lesion* by a period of from four to six weeks.

GROSS PATHOLOGY

Biopsy of these tumors reveals, beneath a raised and perforated periosteum, a pearly-gray and shiny substance of varying consistency: some of it is well formed cartilage, some cystic and hemorrhagic. The various lobules that compose the tumor show a tendency to extend lengthwise up and down the bone and around it, rather than to invade the marrow cavity However in advanced cases, the cortex is broken through, and neoplastic tissue infiltrates the medulla of the bone It is such advanced cases with involvement of the marrow cavity by cartilaginous tumor substance that are most common in the older literature, and for this reason there has been an *erroneous conception* that this type of tumor is of central rather than of periosteal origin (Fig 62)

Small pockets that exude a sanguineous synovial fluid are not rare in these growths. Such cystic areas containing what is a pseudo-joint fluid make the exploration of these neoplasms by one unfamiliar with their pathology an extremely dangerous procedure. Myxomatous tissue contained in the outpouring fluid is the mother substance of these tumors, and is even more readily transplanted than is the myxoma of the benign chondroma (Fig 70)

One of the striking features of the tumor growth is the metastasis or gradual extension into the large veins. H J B Fry* re

Fry H. J B., and Shattock, C. E. Chondrosarcomatous permeation of the inferior vena cava

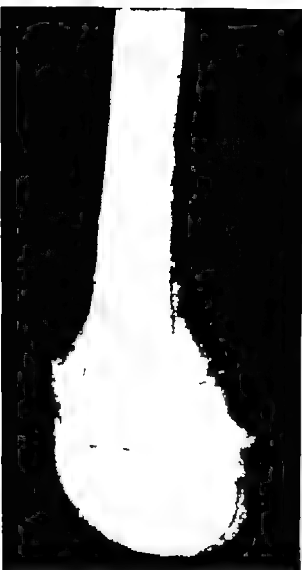


FIG. 63. (No 66337) Roentgenogram of a gross specimen of chondrosarcoma, showing the predominant periosteal location of the new growth.

ported a case in which the tumor arising from the sacrum metastasized to the inferior vena cava and completely filled the right side of the heart with a soft cartilaginous mass. Phemister* reported a similar case in which the cartilaginous growth filled the femoral vein by direct extension from a tumor arising in the femur

In gross specimens, the early lobules of the tumor may be seen sprouting from fibrous strands of a tendon such as the quadriceps in the region where it envelops the patella or the attachment of the adductor magnus at the line of insertion at the adductor tubercle (Fig 71) This relationship



FIG. 64. Cartilaginous exostosis in a child of twelve with incompletely calcified outer margin. These growths must also be distinguished from the benign cartilaginous exostoses occurring in children. In these growths, the cartilaginous portion of the tumor rests on a wider base of periosteal and cortical bone (Fig 34)

and right side of the heart, Brit. J Surg. 14 837 1926.

Phemister D B. Chondrosarcoma of bone Surg Gynec. & Obst. 50: 216, 1930

is particularly striking in some cases and may be verified microscopically by sections from properly chosen areas (Fig 72) Frequently however the tumor has extended sufficiently to obscure its site of origin and no definite conclusions can be drawn from the specimen.

stage this tissue has the full potentialities of subsequent differentiation essential for all of the various structures of the future skeleton Embryologically such a tissue is represented by the perichondrium which although primarily concerned with the proliferation of cartilage, subsequently differ



Fig. 65 (No 26917) Roentgenogram showing an advanced case of primary chondrosarcoma. Note the translucent character of the periosteal growth and the mottled areas in the tibia beneath.

entiates into periosteum and develops the property of direct bone formation. As previously explained, this perichondrium is closely allied or identified with the other types of precartilaginous connective tissue concerned with articular and periarticular functions.

Microscopic Features

The analysis of microscopic sections from a series of cases of primary chondrosarcoma is essentially a study in miniature of the entire embryology of enchondral bone. Here the very earliest stages of cartilage formation from connective tissue can be found as well as the advanced calcifying forms. In addition, but less frequently the phase of substitution bone which follows in the wake of calcified cartilage can be seen in ossification proceeding from early connective tissue This rehearsal of the entire embryology of normal bone in distorted and abortive fashion by chondromyxosarcoma is explicable only on the basis that the tumor tissue represents the earliest type of skeletogenic mesenchyme. At this primitive

The fundamental basis of the pathologic process of primary chondromyxosarcoma is to be found under the microscope in nearly all of the sections taken from this type of tumor Histologically the growth arises from a dense condensation of embryo-like connective tissue. The cells of this tissue, which are either stellate or an elongated spindle shape, give origin to a syncytium (Fig 74) with an increasing amount of clear hyaline-like ground substance in which the connective-tissue cells, after as-

suming a rounded form, become embedded This syncytial tissue is myxomatous, and the scattered rounded cells with small dense nuclei and clear deeply acidophilic cytoplasm are fetal cartilage cells. Later these cells surround themselves with small lacunae, which gradually take a definite capsular form, abutting on the ground substance in a fashion that resembles adult hyaline cartilage. This adult cartilage differs from that found at the normal epiphyseal line and in benign chondromas and osteochondromas in that the cells show less tendency to arrange themselves in definite columns and contain nuclei that are larger more vesicular and more frequently undergoing mitosis. Fibrous septa dividing the cartilage into



Fig. 67 Roentgenogram of a late case of primary chondrosarcoma of the fibula.



Fig. 68 (No 33820) Roentgenogram of a typical primary chondrosarcoma arising at the insertion of the quadriceps tendon in a white girl aged 14 The picture shows a translucent periosteal shadow and the absence of marked medullary or cortical involvement

lobules are also more frequent and far more cellular in these malignant growths. Calcification occurs more sporadically and irregularly While these features are often sufficient to suggest the diagnosis of malignancy they rarely permit a positive diagnosis on the basis of the section alone.

This transition from fibrous tissue to cartilage with an intermediate syncytial or myxomatous stage (Fig 75) has caused this tumor to be called chondromyxosarcoma. Contrary to the traditional views of Ribbert,* Sternberg,† Kolodny,‡ and others,

* Ribbert, H.: Geschwulstlehre für Aerzte und Studierende Bonn, F Cohen, 1904.

† Sternberg, K.: Personal interview with the author July 1929

‡ Kolodny A.: Bone Sarcoma: The Primary Malignant Tumors of Bone and the Giant Cell Tumor Chicago, Surgical Publishing Company 1927



FIG. 68. (No 32485) Roentgenogram of a case of secondary chondromyxosarcoma *arising in a benign osteochondroma. (A) shows the osteochondroma* arising in the lower ramus of the pubic bone. (B) shows the same lesion three years later with definite malignant change Note the granular character of the neoplasm, its immense size and the fracturing of the pubis and the ischium. The patient was a white woman, aged 30 who had known of the presence of the tumor for over three years. Deep roentgen therapy was administered, but the patient died of internal metastases five years after the treatment was begun.



FIG. 69 (No 19419) Specimen of a primary chondrosarcoma in the lower end of the femur of a colored girl, aged 15 The periosteal tumor has invaded the marrow cavity producing a dark cystic area shown in the right hand specimen. The clinical course was extremely brief slightly over three months of symptoms and death within seven months after the primary amputation



Fig. 70 (No 41122) Cysts in the tissue of a primary chondrosarcoma occurring at the tibial tuberosity The patient was a white girl of 17 who complained of pain and swelling of 4½ months duration. She has remained well 9 years after a primary amputation.



Fig 71 (No. 42352) Comparison of the roentgenogram and gross specimen of a primary chondrosarcoma occurring in a white boy aged 20 and treated by amputation.



FIG. 72. Roentgenogram and photomicrograph of a chondrosarcoma arising at the outer end of the clavicle. The primary tumor was in the upper humerus in the greater tuberosity It had been resected two years previously The patient came to autopsy with terminal bronchopneumonia and without metastasis shortly after the roentgenogram was taken.

the myxomatous substance is not a product of cartilaginous degeneration but the predecessor of the later chondral forms which are derived from it, a view that is fully substantiated by the studies herein presented and with which Borst is in full accord.† The mucoid cysts and pockets of syrupy synovial fluid found in association with these myxomatous areas is not a phenome-

Borst, M. Personal interview with the author (C. F. G.) July 1929

† Recent cultures in vitro taken from a leg amputated for chondrosarcoma show that the most active elements are myxomatous, growing from connective tissue of the precartilaginous type.

non of degeneration but concerns the embryologic role which this tissue plays in the formation of normal joint cavities.

Bone formation is not prominent in these primary chondrosarcomas. The osseous tissue is usually next to the periosteum overlying the tumor and is either reactive bone, cartilage and the other toward adult periosteum with the direct production of bone.

It is sometimes extremely difficult to be certain of the presence of chondromyxosarcoma under the microscope and to distinguish these lesions from the more cellular types of benign chondromyxoma. In a

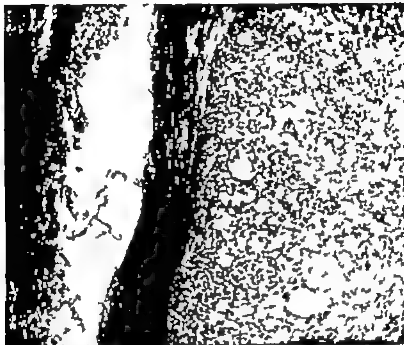


FIG. 73 (P N 27695) Photomicrograph showing the embryonic connective tissue and fetal cartilage cells of a primary chondromyxosarcoma arising from the ends of the tendon. The patient was a colored girl, aged 18, who complained of pain and tumor in the lower end of the femur of four months duration. She died six months after a primary amputation followed by irradiation.

proceeding from normal periosteum, or ossification arising in the dense embryonal connective tissue strands dipping down from the margin of the tumor (Fig. 74) The fact that the latter type of bone, thus produced, is neoplastic in origin and not reactive is substantiated by the finding of similar areas in metastatic nodules of the lung (Figs. 77 and 78) This neoplastic ossification is usually sparse in primary chondromyxosarcoma, but when it does occur it indicates that the primitive perichondrium or precartilaginous connective tissue from which these growths arise is differentiating in two directions, one toward the proliferation of review of many sections, the cellular nature of the connective tissue strands, the presence of fetal cartilage, the malignant nuclei of the cartilage cells and the occasional presence of cellular areas containing round cells midway between fetal cartilage and chondroblasts in differentiation (Fig. 79) have been found helpful in identifying chondromyxosarcoma.

HISTOGENESIS

From the standpoint of histogenesis, it is evident that this form of chondrosarcoma is related by location and by structure to primitive precartilaginous tissue. Its occur

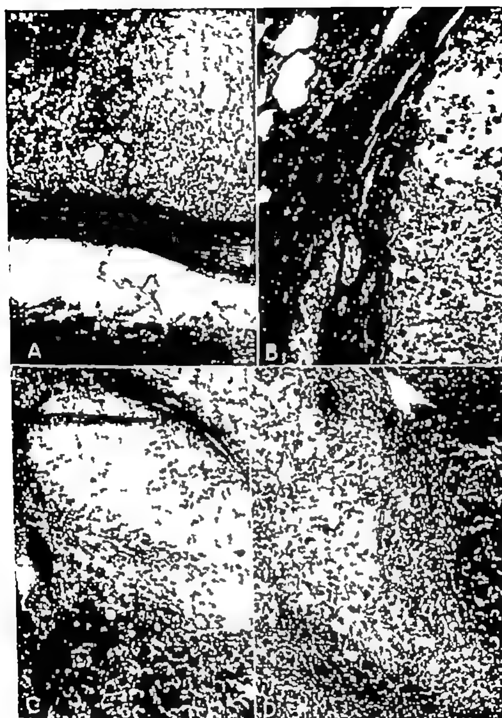


FIG. 74. Studies showing the cycle of tissue differentiation in chondromyxosarcoma. (A) shows primitive connective tissue and fetal cartilage cells arising from a tendon adjoining the tumor. This is the myxomatous stage. (B) is from a metastatic lung nodule in a case of chondromyxosarcoma and shows the more adult cartilage cells developing in a myxomatous matrix. (C) shows the margin of the tumor in a case of chondromyxosarcoma in which the primitive precartilaginous connective tissue is giving rise to adult and calcifying cartilage. This is the cartilaginous stage. (D) is from the central portion of a chondromyxosarcoma and shows the primitive connective tissue in the tumor giving rise to direct bone formation.

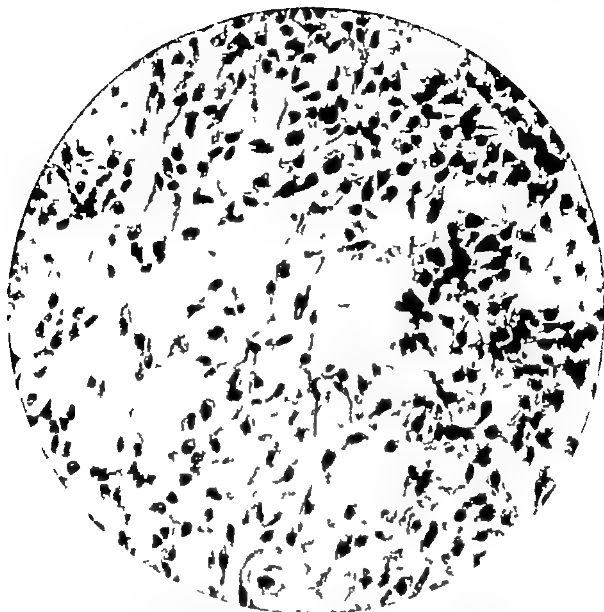


FIG. 75. (No. 27695) High-power photomicrograph of the lesion depicted in Figure 73. This illustrates clearly the differentiation of fetal cartilage cells from the spindle cells forming the so-called myxoma In the lower part of the picture there is shown an early cartilage cell secreting a capsule about itself The cartilaginous tissue in this case is clearly proliferated from the preceding myxomatous state, contrary to the traditional views that the myxomatous tissue is a degenerate product of cartilage.

rence at the sites where tendons attach directly to bone indicates that the devel opmental steps from connective tissue to cartilage to bone persist normally in these regions. Adequate evidence to substantiate such a conclusion has been presented in tracing the histogenesis of the benign exos toses (see p 66 Histogenesis)

This relatively undifferentiated fibrous tissue persisting at the sites where chondromyxosarcomas arise does not necessarily represent fetal-cell rests in the sense of Cohnheim,* although this form of sarcoma may arise centrally from cartilaginous rests within the marrow cavity The evidence

Cohnheim, J: Vorlesungen über allgemeine Pathologie, Ein Handbuch für Aerzte und Studierende, Berlin, 1877–1880.

duced here favors the view that the persistence of this tissue about periarticular joints provides a normal growth center which functions in maintaining tendon length in keeping with increased skeletal growth. This would account for the origin of these primary forms of ossifying chondrosarcoma during the age period of maximum skeletal growth and would indicate that the normal cytologic transitions accompanying tendon growth form a fundamental basis for the origin of this tumor. This conclusion that both normal growth impetus and a normal cycle of histogenic differentiation at a growth center is essential to the inception of this form of sarcoma of bone is substantiated by the study of the other types of osteogenic sarcoma which arise under similar circumstances.



FIG. 76 Chondrosarcoma with radiolucent periosteal tumor growth and characteristic honeycombing of the cancellous spaces.

The close similarity between the mode of origin of the benign exostoses and the primary chondromyxosarcomas raises the question concerning the factors which determine whether a given neoplasm will pursue a benign or malignant course. For it is fairly certain that at their inception the developmental state of the mother tissues is practically the same for both benign osteochondromas and the malignant primary

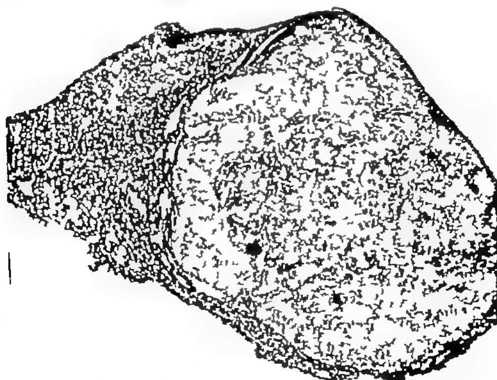


FIG. 77 (No. 31523) Low-power photomicrograph of a metastatic nodule in the lungs of a patient dying of chondromyxosarcoma.

chondrosarcomas Why therefore, should the exostosis be such a slowly growing and benign affair and the chondromyxosarcoma, with the same beginning, pursue such a rapid and malignant course?

mesenchyme at the tumor site. This excessive accumulation of germinal tissue or mother substance at the tumor's inception is probably brought about by similar factors in both benign and malignant forms.



FIG 78. (No. 31523) Higher magnification of lung nodule shown in Figure 77 The new bone depicted in the high-power illustration shows clearly the power of bone formation residing in the primitive connective tissue found in this form of neoplasm.

Pathologic study of these growths permits us to pursue this problem only to a limited extent. In both benign osteochondromas and in chondrosarcomas there is an excessive proliferation of skeletogenic

Undue tension by unequal bone and tendon growth produces a disturbance in the cement substance of the skeletogenic tissue (see p. 75) at the point where tendons attach to bones. Accompanying this dis-

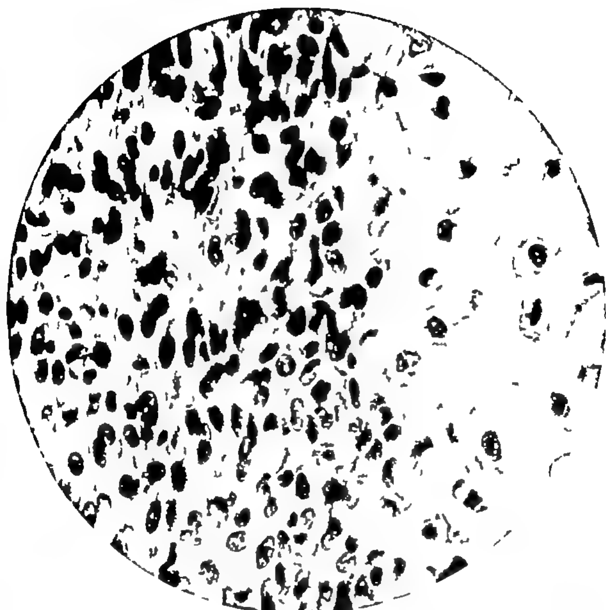


FIG. 79 (No. 20116) Photomicrograph showing the cellular areas containing round cells midway between fetal and adult cartilage, characteristic of chondromyxosarcoma as distinguished from the benign chondroma.

turbance of cement substance there is a proliferation of intermitotic cells of the precartilaginous connective tissue. Following this accumulation of intermitotic cells, there is, in the benign growths, differentiation of the developing chondrogenic tissues which is proportional to the availability of prechondral intermitotic cells. In chondral sarcomas, on the other hand, the maturing influence present in osteochondromas is lacking or deficient. Presumably this is because it is drained away from the tumor site by normal skeletal growth or because the tissue is segregated from its influence by an impermeable tissue layer such as the outer fibrous layers of the periosteum or the cortical bone.

PROGNOSIS AND TREATMENT

Permanent cures, even when amputation is performed promptly without a previous exploration, are rare in primary chondrosarcoma. In a fatal case the patient usually lives approximately 14½ months after oper

chondrosarcomas. Why therefore, should the exostosis be such a slowly growing and benign affair and the chondromyxosarcoma, with the same beginning, pursue such a rapid and malignant course? mesenchyme at the tumor site. This excessive accumulation of germinal tissue or mother substance at the tumor's inception is probably brought about by similar factors in both benign and malignant forms.

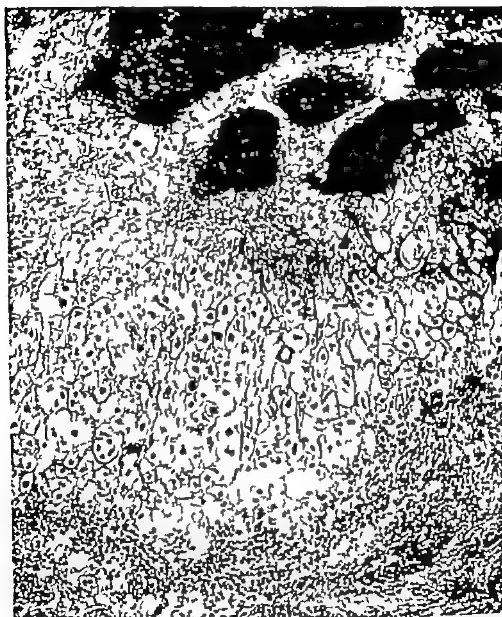


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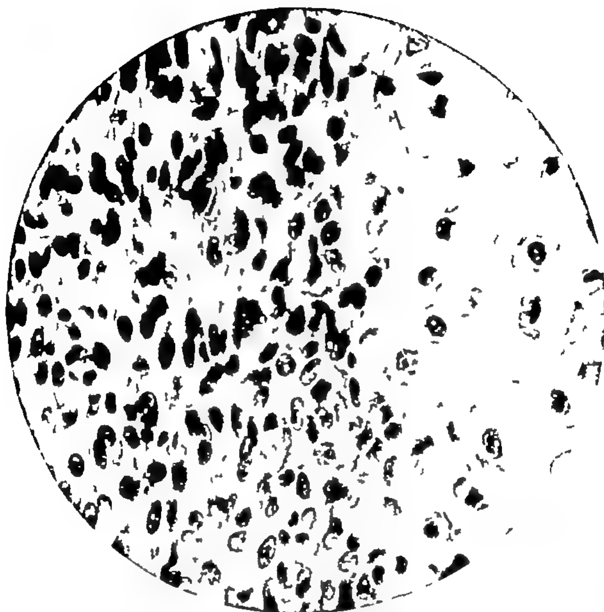


Fig. 79 (No. 20118) Photomicrograph showing the cellular areas containing round cells midway between fetal and adult cartilage, characteristic of chondromyxosarcoma as distinguished from the benign chondroma.

turbance of cement substance there is a proliferation of intermitotic cells of the precartilaginous connective tissue. Following this accumulation of intermitotic cells, there is, in the benign growths, differentiation of the developing chondrogenic tissues which is proportional to the availability of prechondral intermitotic cells. In chondral sarcomas, on the other hand, the maturing influence present in osteochondromas is lacking or deficient. Presumably this is because it is drained away from the tumor site by normal skeletal growth or because the tissue is segregated from its influence by an impermeable tissue layer such as the outer fibrous layers of the periosteum or the cortical bone.

Prognosis and Treatment

Permanent cures, even when amputation is performed promptly without a previous exploration, are rare in primary chondrosarcoma. In a fatal case the patient usually lives approximately 14⅞ months after oper

ation. Since the average duration of symptoms prior to operation is 5½ months, a case of primary chondrosarcoma can be expected to run its entire clinical course within 20 months. Neither the age nor the location of the growth greatly influences the ultimate results, although apparently the prognosis is somewhat worse for children and when the lesion is in the upper end of the humerus or of the femur. Delay with prolongation of symptoms previous to operation accompanied by destruction of medullary bone diminishes the prospect of a cure. Incomplete initial surgical treatment must be looked on unfavorably but one cure was accomplished despite delay and recurrence after an initial operation.

If there is failure in the operative procedure primary chondrosarcoma shows a marked tendency to recur locally as well as to metastasize. The total number of cures in the 103 cases adequately followed was 15 (Table 11). In the cured cases amputation was performed, this procedure following after radium treatments in two cases.

Deep roentgen therapy either preceding the operation or given postoperatively has no influence on the results as far as can be determined from this series of cases. When the patient has refused operation deep roentgen therapy has apparently been helpful in alleviating pain, except in the more advanced stages of the disease. Its use, however, cannot be considered other than palliative in the dosages ordinarily administered. Radical resection, when used alone, has not been successful in accomplishing a cure. In lesions of the skeletal trunk radical excision or resection, followed by thermal cauterization, is worthy of a trial.

TABLE 11 RESULTS OF TREATMENT IN CASES OF PRIMARY CHONDROSARCOMA

Total number of cases followed	114
Number of cases well less than five years	11
Total number of fatal cases	88
Number of patients living over five years	15
Percentage of five-year cures	15%

SUMMARY

A periosteal osteogenic sarcoma containing cartilage and known as chondromyxosarcoma or chondrosarcoma may arise primarily in young patients at the sites where tendons insert directly into bone. The most frequent ages for the appearance of these chondrosarcomas are between the years of 14 and 21. The favorite sites are about the knee, at the line of the insertion of the adductor magnus, in the lower femur or in the upper tibia where the tendon of the quadriceps attaches. The symptomatology is brief—about six months in duration—and is characterized by pain, tumor and dysfunction. The neoplasm is composed of a cartilaginous mass, accompanied by ossification and a small amount of mucoid degeneration. In the roentgenogram it is faintly visible as a subperiosteal shadow with an infiltrating outward margin which may be streaked by a few spicules of calcified or ossified material. The tumor does not involve the cortex or medullary cavity until late in the disease, when it invades these areas and bone destruction is the result. Histologically these chondromyxosarcomas are characterized by a transition of connective tissue to myxoma and thence to fetal and adult cartilage followed by bone formation. They are abnormal proliferations of precartilaginous connective tissue which forms a tissue of union and a growth zone between the ends of tendon and normal bony protuberances and thus from an embryonic standpoint are closely allied to the benign exos-

toses. Permanent cures in the primary chondromyxosarcomas average about 15 per cent. Amputation radical excision or resection is the method of choice in treatment. The usual clinical course of the primary form terminates fatally within the space of 20 months.

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6

Osteogenic Sarcoma–Secondary Chondrosarcoma

CLINICAL FEATURES
ROENTGENOGRAPHIC FEATURES
PATHOLOGY AND HISTOGENESIS
PROGNOSIS AND TREATMENT
SUMMARY

In the benign tumors of the osteochondroma and chondroma groups, the persistence of connective tissue of the embryonic precartilaginous type makes possible the origin of secondary chondrosarcoma which is superimposed on the original benign growth.

In many of such secondary lesions evidence of the pre-existent growth is easily traced (Fig 80) but in others, in which an obscure and latent defect has been present for many years within the tuberosity of a long bone, urgent symptoms are not manifest until the condition has taken on frankly sarcomatous features.



Fig 80 (No 44148) Transformation of an exostosis into secondary chondrosarcoma. The primitive connective tissue and chondral elements in the exostosis which is clearly visible in (A) are proliferating, giving rise to the infiltrative malignant lesion shown in (B) (A) and (B) are roentgenograms of identical lesions in the same patient taken six weeks apart. This secondary chondrosarcoma shows a degree of malignancy intermediate between that of the benign exostosis and that of primary chondrosarcoma.

Attention was called to the latter type of



FIG. 81 (No. 6773) Secondary malignant change occurring in a benign exostosis. The cap of the lesion has been blotted out, and the base of the outgrowth has been invaded by the destructive process of the chondrosarcoma The patient was a white woman, aged 53 who had had a tender spot and a swelling on the shaft of the left humerus for over 20 years. She had noticed an increase in the lump for only 9 months, with increased pain at this site There was a history of syphilis dating back 26 years. This tumor was excised by Halsted seven times within 7 years, the final recurrence necessitating amputation at the shoulder joint. Three years after the amputation and ten years after the first operation, death occurred with metastases to the scalp and mediastinum. The microscopic structure of the tumor is shown in Figure 103

tumor by Bloodgood in 1906 under the term of pure myxoma of bone While not considered primarily malignant, these lesions usually resulted in death from metastases after repeated recurrences over a period of years. To this clinical entity of Bloodgood, a secondarily malignant origin may now be ascribed on the basis of a re-

Bloodgood, J. C.: Bone tumors, pure myxoma of bone, Prog. Med. 4 221, 1906

study of all the cases thus classified by him. These tumors occur most frequently in pa tients over 30 years of age and in the roent genogram usually have the structure of a benign chondroma at their base within the bony tubercle but outwardly the translucent and indefinite shadow of a chondromyxo-sarcoma (Fig 81)

this tendency to transplantation and metastasis is more slowly manifested than in other tumors but nevertheless these do oc cur Ferguson s impression that repeated local operations with late amputation served to increase the number of surviving cases of osteogenic sarcoma was influenced by the number of secondary chondrosar

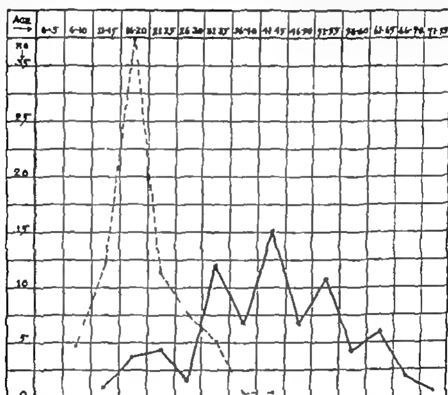


CHART ▮ Age distribution in cases of secondary chondromyxosar coma. The broken line shows the incidence in 79 cases of primary chondromyxosarcoma the solid line, in 75 cases of secondary chondromyxosarcoma

comas included in his series. It is the low-grade nature of the malignancy of these cartilaginous growths and not the inadequate surgical procedures that accounts for their long survival This is best emphasized by comparing the duration of preoperative symptomatology with the postoperative survival The slower preoperative course characteristic of cartilaginous tumors which undergo malignant change is indicative of their lower degree of malignancy and in turn is reflected in their long postoperative survival. The sarcomas which are from a histologic standpoint more highly malig

Because many of these growths do not show malignant tendencies until multiple incomplete excisions have been performed, some authors have believed that their sar comatous nature has been partly suppressed by these half hearted measures (Fergu son) The reverse is the case All forms of osteogenic sarcoma are aided in their spread and invasive tendencies by partial excision or incision. In these secondary chondrosarcomas when the transformation from a preceding benign growth occurs,

Ferguson, A B. Treatment of osteogenic sar coma, J Bone & Joint Surg, 22 96 1940.

nant have a shorter course and a shorter survival period. The method of treatment is of secondary importance compared with the fundamental biologic behavior. Since all methods of treatment for sarcoma of bone to date are relatively ineffective, the vast majority are lost, not saved.

CLINICAL FEATURES

Most of these tumors occur in persons between the ages of 35 and 55 (71 per cent) with the peak of incidence between the ages of 40 and 45. They may, however, occur before the age of 30 (Chart 5). The location of these neoplasms differs from the primary form of chondrosarcoma in that there is a greater tendency for them to occur centrally at the upper end of the humerus, about the ribs and at the heel (Fig. 82). The total duration of symptoms averages over 8 years in this series, varying from 2 to 25 years.

When this sarcoma develops secondarily in a benign cartilaginous growth, the history of the earliest phases of the disease can usually be elicited by careful questioning. The typical story given by such patients may begin with an injury many years before, the effects of which have subsided without apparent trace, or have remained in the form of a persisting lump of stationary size. There may be a history of rheumatic pains for many years or the consciousness that the affected limb has always been crooked or shorter than the corresponding normal member. After an interval of years, and with or without obvious provocation, pain, swelling or pressure phenomena will cause an exacerbation of the previous trouble and lead the patient to consult his physician. In one instance, a farmer had been kicked in the pubic region by a horse 25 years before, and a small stationary tumor had developed. In the 2 months preceding examination, a rapidly growing pelvic mass (arising from the pubic bone near the symphysis) had caused pain and edema in the left leg because of blockage of the venous return. A similar case of sarcoma in a woman 50 years of age occurred 20 years after the onset of rheumatic pains in the upper part of the arm near the deltoid muscle at the site of an old exostosis.

Secondary chondrosarcoma arises most frequently on the basis of preexisting central chondroma in a large bone. The tendencies for such cartilaginous tumors to undergo malignant change has been stressed in Chapter 4, p. 102. Frequently the central growth is present as persistent embryonic cartilaginous tissue in the marrow cavity which has given no previous symptoms. Malignancy of this character also complicates single and multiple ex

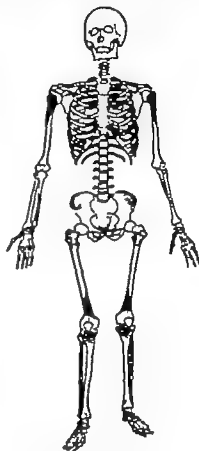


Fig. 82. Incidence of secondary chondromyxosarcoma according to skeletal location. The solid black areas indicate the most frequent sites; the checked areas, the common sites; the diagonal lines, the occasional or rare sites.

TABLE 12. SECONDARY CHONDROSARCOMA

Pathologic No	Race	Sex	Age	Location	Duration	Symptoms	Roentgenographic Appearance	Treatment	Microscope Changes	Results of Treatment
62374	W	M	36	Femur neck	3 mos.	Pain and limitation of motion	Lesion in region of femoral neck	Surgery	Cartilage formation	Dead 1 yr
62302	W	M	41	Scapula	8 mos.		Destructive process, expansion of coracoid process	Biopsy	Chondrosarcoma	Living 7 yr
62268	W	F		Humerus, left		Pain and stiffness		Resection	Fetal cartilage and myxoma	Dead 2 yr
62224		M		Sacroiliac, right		Soreness		Biopsy irradiation	Chondrosarcoma	Dead 4 yr
60830	W	M	45	Leg, especially calcaneus		Atrophic since birth	Tibia invaded sun ray tumor extending out from calcaneus	Disarticulation of hip joint	Lobules of adult hyaline cartilage	Dead 2 yr pneumonia
59682	W	F	50	Acromioclavicular joint				Exploration	Fetal cartilage, myxoma	Lost
50454	W	M	21	Femur right	1 yr	Unable to walk	Tumor with smooth outline attached to linea aspera	Operation	Cartilage with cellular strands of connective tissue	Lost
50372	W	F	[illegible]	Femur left		Pain and swelling		Amputation		Dead 6 mos.
50310	W	F	[illegible]	Ischium		Temperature and pain	Destruction of ischium	Amputation	Lobules of fetal and hyaline cartilage	Dead 1½ yr
57444	W	F	[illegible]	Vertebra		Pain	Involvement of 8th 9th and 10th thoracic vertebra		Masses of adult cartilage	Dead 1 yr
56906	W	M	67	Ischium	5 mos.		Irregular areas of calcification invasion of soft parts			Lost
55230							Adult with Paget's disease		Malignant connective tissue with islands of cartilage	Lost
55052	W	F	24	Medial aspect of tibia	3 mos.		Multilocular defect extending into soft parts	Puncture biopsy		Well 13 yr

55910	W	F	18	Femur right lower			Partially calcified rounded mass destroyed pubis		Chondrosarcoma	Lost
55470	W	F	20	Femur	8 yr		Areas of abnormal calcification periosteal roughening		Chondrosarcoma	Slow growth 5 yr later
55148	W	M	55	Ilium left	2 yr		Osteochondroma like mass attached to wing of ilium malignant proliferation extending to trochanter	Irradiation	Chondrosarcoma	Little growth in 3 yr
53994	W	F	75	Skull	5 wks.		Wooly fuzziness of Paget's disease	Local excision	Chondrosarcoma	Dead 3 mos.
53702	W	F	20	Femur			Multiple exostoses overlapped by periosteal new bone destroying contours	Biopsy	Chondrosarcoma	Well 3 yr
53710	W	M	17	(Epiphysis) tibia	18 mos		Bone destruction calcareous stippling	Biopsy irradiation	Chondrosarcoma	Slow progress of lesion 2 yr W 11.5 yr
51109	W	M	21	Scapula	1 mos		Rounded exostoses, fractured periosteal reaction	Excision 3-1-32	Chondrosarcoma	
51188	W	M	31	Femur	6 yr			Amputation ? 1933	Chondrosarcoma	Well 6 yr
51161	W	M	72	Femur	5 yr		Central bone destruction with spotty calcification		Chondrosarcoma	Lost
50021	C	M	52	Femur	8 mos			Excision	Chondrosarcoma	Dead 9 mos.
10108		F	63	Femur lower right	18 mos		Areas of resorption about calcified lesion	Amputation		W 11.3 yr
10382	W	M	71	Ilium	2 yr			Irradiation	Chondrosarcoma	Dead 1 yr
17868	W	M	52	Lumbar	18 mos			Excision	Paget's disease	Dead 7 mos.
10150	W	F	53	Femur	6 mos			Amputation	Chondrosarcoma	Dead 2 yr
10000	W	M	35	Pelvis	7 mos			Excision	Chondrosarcoma	Well 3 yr
16338	W	F	30	Femur	1 yr			Amputation	Chondrosarcoma	Well 6 yr

TABLE 12 SECONDARY CHONDROSARCOMA (*Continued*)

Pathologic No	Race	Sex	Age	Location	Duration	Symptoms	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
45364	W	M	30	Tibia	6 mos.			Irradiation	Chondrosarcoma	Well 3 yr
45002	W	F	39					1931	Secondary to exostosis	Autopsy
44899	W	M	7	Ilium	1 mo			Excision	Chondrosarcoma	Well 11 yr
44798	W	M	26	Ilium	2 yr			Excision	Secondary to exostosis	Dead 4 yr
44344	W	M	40	Scapula	2 yr			Amputation	Chondrosarcoma	Dead 1 yr
43910	W	M	45	Pelvis	18 mos.			Excision	Chondrosarcoma	Dead 1 yr



FIG 83 (No 34522) Illustrations of a case of secondary chondrosarcoma arising in a chondromatous lesion in the internal condyle of the left femur The condition had caused symptoms for over 20 years. The patient died of metastasis 10 years after the exploratory operation in spite of amputation well above the knee This roentgenogram (Fig. 83) shows the calcified lesion in the femoral condyle before the malignant properties of the tumor became manifest The film was taken 10 years before death of the patient (November 1920)

ostoses and is probably more common in the multiple hereditary form. Malignant change in bones the seat of Paget's osteitis deformans is most commonly secondary chondrosarcoma.

The onset of malignancy in such cases does not precede the onset of the acute symptoms by many months. However the clinician must be on his guard against making a diagnosis of benignancy because of the long duration of the symptoms. The degree of pain and the rapidity of growth are more trustworthy guides. It must be borne in mind however that benign exostoses which have been subjected to incomplete operation may rarely show similar features on recurrence It is a good clinical rule to suspect a secondary chondromyxosarcoma, in the presence of a possible cartilaginous lesion of bone in an adult, when a



FIG. 84. (No. 34522) Lateral view of the lesion shown in Figure 83 taken three years later (January 1924) and showing the invasive and malignant character of the growth. Note the persistence of the old calcified area in the condyle.



FIG. 85 (No 34522) Anteroposterior view taken at the same time as Figure 84.

history of indefinite rheumatic pains for a period of from 5 to 10 years is followed by a change in the character and intensity of the symptoms (Fig 83)

This is well illustrated by a recent case of a physician, 31 years of age, who had a lesion in the internal malleolus of the left tibia (Fig 89) From a roentgenographic standpoint, this tumor was diagnosed a benign giant-cell tumor The location in an epiphysis, the central area of destruction and the age of the patient were consistent with such a diagnosis. However the patient gave a history of injury and continued weakness with occasional rheumatic pains in the left ankle dating back nineteen years. The acute symptoms of stiffness and soreness had been present only six weeks This history suggested a secondary chondromyxomatous lesion which was verified at operation

Trauma, incident to the malignant change occasionally occurs in this group of tumors, but often the injury relates to the original benign growth and is to be associated with the incidence of trauma found in exostoses and kindred lesions (from 30 to 40 per cent) Pathologic fracture occurs in 6 per cent of secondary chondrosarcomas, and in these cases the line of fracture often extends through the protruding tumor mass rather than through the body of the bone (Fig 90)

ROENTGENOGRAPHIC FEATURES

The most easily recognized secondary chondrosarcoma is that in which distinct evidence of the nature of the primary lesion

TABLE 13. SECONDARY CHONDROMYXOSARCOMA

Pathologic No.	Race	Sex	Age	Location	Duration, y	Symptoms	Primary Condition	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
42831	C	F	22	Fibula, upper	4	Tumor; pal	Osteochondroma	Granular periosteal new bone	Resection; irradiation	Chondromyxosarcoma	Well 6 yr later
43604	W	M	37	Humerus	1				Amputation	Chondromyxosarcoma	Dead 2 yr
43255	W	M	25	Femur greater trochanter	8	Tumor	Chondroma	Trochanter destroyed medulla rarefied	Excision	Chondromyxosarcoma	Dead
43253	W	M	30	Lower end of femur			Chondroma		Amputation	Chondromyxosarcoma	Dead 4 mos. late
42888	W	M	30	Humerus, upper	2	Pain; tumor	Chondromatosis	Bone expansion; new bone formation	Resection	Chondromyxosarcoma	Dead after operation
42704	W	M	28	Ilium	2 mos.				Excision	Chondromyxosarcoma	Dead 9 mos.
42300	W	M	50	Pubis, left	28	Trauma, tumor; pain; edema	Osteochondroma	Granular periosteal new bone	Irradiation		Dead
42236	W	M	31	Os calcis fibula, lower	9	Pain, tumor	Osteochondroma at old fracture site	Large translucent mass about achilles tendon	Exploration; amputation	Chondromyxosarcoma	Well 5 yr
42229	W	M	40	Femur lower	22	Trauma; pain; tumor	Exostoses chondromatosis in and about knee joint	Multiple exostoses joint mass; translucent periosteal shadow	Curettement, amputation	Chondromyxosarcoma	Well 1 yr later
42282	W	M	47	Rib, third anterior	7	Tumor	Chondroma	Expanded costochondral junction; translucent periteal shadow	Resection (3 times)	Chondromyxosarcoma	Three recurrences; dead after 6 yr
42254	W	M	19	Tibia, upper		Tumor, congenital (?) recent pain	Osteochondroma	Pedicle exostoses undergoing destruction and proliferation	Exploration (3 times) amputation	Chondromyxosarcoma	Living 21 mos.
42286	W	M	41	Ischium		Tumor; pain	Osteochondroma	Secondary bone destruction in exostosis	Curettement	Chondromyxosarcoma	Recurrence
41850	W	M	33	Humerus, greater tuberosity	8	Tumor	Chondroma	T berosity destroyed; sarcoma rarefied	Amputation	Chondromyxosarcoma	Well 11 yr later
41103				Dura, crest					Excision	Chondromyxosarcoma	Recurrence
40778	W	M	30	Tibia, upper	2	Pain; tumor; pathologic fracture	Osteochondroma	Translucent periosteal shadow; bone destruction beneath	Curettement (3 times); irradiation; radium and toxins	Chondromyxosarcoma	Well 12 y
40643	W	M	15	Metatarsal base, second	2	Tumor; trauma	Chondroma	Central destruction; periosteal roughening	Excision	Chondromyxosarcoma	Dead 1 yr later
40808	W	M	21	Femur lower left toes right foot	3	Multiple tumors elephantiasis	Chondroma (?)	Diffuse translucent periosteal shadow; rarefaction of phalanges	Amputation, left leg and right foot	Chondromyxosarcoma	Dead 4 mos. later
40480	W	M	30	Popliteal space	15	Trauma; tumor; pain	Chondromatosis	Translucent shadow of soft part	Excision	Chondromyxosarcoma	Well 2 mos.
40373	W	F	54	Femur lower		Tumor	Osteochondroma (?)		Exploration	Chondromyxosarcoma	Lost
40184	W	F	63	Scapula, left	14	Tumor; pain			Irradiation; colloidal lead; amputation	Chondromyxosarcoma	Recurrence 3 yr later Dead 4 y; [illegible] 3 yr later
39943	C	M	18	Femur lower left	3	Trauma; tumor	Osteochondroma	Rounded exostosis; translucent shadow of soft part two bone	Amputation	Chondromyxosarcoma	

37646	W	F	37	Femur lower left	3	Trauma tumor	Chondroma	Translucent periosteal shadow; new bone formation	Excision; amputation	Chondromyxosarcoma	Recurrence; well 6 yr
37963	W	M	29	Femur upper	6	Tumor	Osteochondroma	Granular periosteal new bone	None		Dead 3 mos. later
37834	W	M		Skull, occipital		Tumor	Chondroma		Excision	Chondromyxosarcoma	Well 9 yr later
37218		M	35	Upper end of humerus		Trauma tumor		Periosteal bone formation	Partial resection	Chondromyxosarcoma	Recurrence; dead 4 yr after operation
37114	W	F	30	Ribs, right	1	Tumor; pain	Chondroma		Resection	Chondromyxosarcoma	Discharged well
37022	W	F	49	Humerus, upper right	4	Trauma; tumor; pain	Osteochondroma	Translucent periosteal shadow	Resection	Chondromyxosarcoma	Well 13 yr
35944	W	M	42	Femur trochanter	20	Tumor; pain	Osteochondroma	Bone destruction; translucent periosteal shadow	Curettement	Chondromyxosarcoma	Recurrence
35414	W	M	19	Femur lower	9	Pain; swelling	Osteochondroma	Translucent periosteal shadow with bone destruction	Amputation advised		Well 6 yr later
34615	W	M	49	Femur lower left	2	Pain; pathologic fracture	Chondroma	Translucent periosteal shadow; rarefied bone beneath	Curettement, irradiation	Chondromyxosarcoma	Well 6 yr
34560	W	M	30	Femur lower shaft	4	Pain; swelling; tumor		Exostosis and shadow of soft part	Excision; amputation; irradiation	Chondromyxosarcoma	
34535	W	F	41	Femur, lower left	23	Trauma; stiffness; pain	Chondroma	Translucent periosteal shadow; bone destruction beneath	Exploration; amputation	Chondromyxosarcoma	Metastases to frontal bone 4 yr later
34300	W	F	30	Fibula, lower	1	Tumor	Chondroma	Cystic area of bone destruction	Curettement	Chondromyxosarcoma	Lost
34250	W	M	49	Ilium, right	3	Pain; stiffness	Chondroma	New bone; bone destruction	Excision; radium	Chondromyxosarcoma	Dead 3 yr later
34106	W	M	51	Pelvis, acetabulum	1	Trauma; pain; tumor	Osteochondroma	Rarefaction; expansion of acetabular margin	No operation	Chondromyxosarcoma	Dead 4½ yr later; autopsy
33472	W	M	48	Femur greater trochanter right	2	Trauma; pain	Chondroma	Translucent periosteal shadow; bone destruction beneath	Curettement (13 times); amputation	Chondromyxosarcoma	Dead 4 yr later
33158	W	M	55	Femur	6				Amputation	Chondrosarcoma	Well 11 yr
33062	W	M	23	Tibia, upper shaft	1½	Trauma; pain; pathologic fracture	Chondroma	Translucent shadow of soft part	Exploration; resection; irradiation	Chondromyxosarcoma	Well 7 yr later
33008	W	F	75	Humerus, upper right	4	Pain; tumor	Chondroma	Translucent periosteal shadow; bone destruction beneath	No operation	Chondromyxosarcoma	Dead 3 yr later; autopsy
27068	W	M	59	Tibia, upper left	1	Pain; tumor	Chondroma	Translucent periosteal shadow of tuberosity; diffuse bone destruction of upper shaft	Many curettings; amputation	Chondromyxosarcoma	Well 3 yr
32483	W	F	30	Ischium, right	3	Tumor pathologic fracture	Osteochondroma	Granular periosteal new bone	Irradiation		Dead 5 yr later
32317	W	M	29	Femur mid right	1½	Trauma; swelling, pain; tumor		Large calcifying periosteal tumor (exostosis)	Exploration; amputation	Chondromyxosarcoma	Suicide 3 yr later
30344	W	F	25	Pubis, right	3	Pain; tumor	Osteochondroma	Bone destruction; translucent periosteal shadow	Curettement	Chondromyxosarcoma	Recurrence

TABLE 13. SECONDARY CHONDROMYXOSARCOMA (*Continued*)

Pathologic No.	Race	Sex	Age	Location	Duration, yr	Symptoms	Primary Condition	Roentgenographic Appearance	Treatment	Microscopic Changes	Results of Treatment
30240	W	M	20	Femur, lower	3	Tumor		Metaphyseal (dealing) periosteal tumor	Exploration	Chondromyxosarcoma	Dead 1 yr 3 mo later
30248	W	M	30	Femur, lower	3	Tumor	Osteochondroma (?)		Exploration	Chondromyxosarcoma	Dead 11 mos. later
30186	W	M	40	Femur, lower				Rarefaction and cortical expansion of shaft	Amputation		Well 5 yr lost
29819	W	M	19	Astragalus	4	Pain tumor	Chondroma	Bone destruction radiating new bone	Exploration; amputation	Chondromyxosarcoma	Well 5 yr after amputation
29816	W	M	64	Tibia, fibula; pelvis	½	Trauma pain	Ossifying periostitis Paget disease (?)	Ossifying periostitis; translucent mass in popliteal space	Irradiation; amputation		Dead 7 mos. later
29813	W	F	54	Femur, lower	½	Pain; tumor	Osteochondroma	Translucent periosteal shadow over exostosis	Excision (?)		Lost
29580	W	F	53	Humerus, upper	1	Tumor; pain	Osteochondroma	Granular periosteal new bone	Excision; irradiation	Chondromyxosarcoma	Dead 1 mo. later
29467	W	M	29	Humerus, midshaft		Tumor and tenderness	Osteochondroma	Translucent periosteal shadow; bone destruction	Resection, roentgen therapy		Well 7 yr 5 mo.
29093	W	M	43	Ilium, acetabulum	½	Trauma; pain	Osteochondroma	Periosteal roughening; bone destruction beneath	Curettement; radium	Chondromyxosarcoma	Dead 9 mos. later
28639	W	F	55	Tibia, upper	½	Pain, tumor	Chondroma	Translucent periosteal shadow	Amputation	Chondromyxosarcoma	Dead 2 yr later
28533	W	M	45	Humerus, upper	20	Pain		Tremendous bone destruction; multiple periostitis		Chondromyxosarcoma	Dead; metastasis to bone and lungs
28412	N	F	17	Ninth rib	4	Pain; tumor	Chondroma		Resection (twice)	Chondromyxosarcoma	Well 9 yr after second operation
28306	W	F	8	Tibia, upper	20		Osteochondroma	Translucent periosteal shadow; bone destruction beneath	Curettement; radium	Chondromyxosarcoma	Well 11 yr
28246	W	F	41	Vertebra, fourth lumbar	41	Congenital multiple tumors	Multiple chondromas, hereditary	Translucent periosteal shadow; bone destruction; multiple exostoses	Exploration		Dead 2 yr later
27791	W	M	24	Scapula; spine	7	Trauma tumor	Chondroma	Rarefied expanded area; bone destruction beneath	Curettement	Chondromyxosarcoma	Lost
27298	W	M	44	Femur shaft	1/12	Trauma, tumor			Amputation	Chondromyxosarcoma	Well 20 yr later
27283	W	F	33	Rib at sternum	1	Tumor	Chondroma		Curettement (3 times); radium	Chondromyxosarcoma	Recurrence, lost
26731	W	M	43	Humerus, upper	3	Pain tumor	Chondroma	Translucent periosteal shadow; bone destruction beneath	Irradiation; resection; amputation	Chondromyxosarcoma	Dead 20 mos. later
23805	W	F	70	Femur, lower	½	Pain; tumor	Osteochondroma	Granular periosteal new bone	Amputation	Chondromyxosarcoma	Dead 1 yr later
22234	W	F	42	Femur, lower	24	Tumor	Osteochondroma chondrodysplasia	Bone expansion granular periosteal new bone			Dead 1 yr later

22929	W	M	40	Astragalus	30	Trauma; tumor; pain	Osteochondroma	Translucent periosteal shadow with new bone	Resection amputation	Chondromyxosarcoma	Dead 3 yr later metastasis to other bones
19344	W	M	43	Os calcis	1	Pain, tumor	Osteochondroma	Translucent periosteal shadow	Curettement; amputation	Chondromyxosarcoma	Recurrence; living 3 yr
18133	N	M	37	Humerus, upper	8	Pain tumor	Chondroma	Bone expansion; translucent periosteal shadow	Amputation (2 times)	Chondromyxosarcoma	Dead 10 mos. later
17780	W	M	34	Pelvis	1	Tumor	Osteochondroma	Granular periosteal new bone	Resection	Chondromyxosarcoma	Died at operation
15977	W	F	60	Tibia, shaft	3	Tumor pain	Paget disease	Osteitis deformans; translucent periosteal shadow; bone destruction	Amputation	Chondromyxosarcoma	Dead 7 mos. later
15305	W	M	49	Sternum, upper	3	Tumor			Partial excision	Chondromyxosarcoma	Well 9 yr later
14327	W	M	28	Humerus, upper	3	Trauma, pain; tumor; previous abscess	Chondroma	Translucent periosteal shadow; new bone; bone destruction	Amputation	Chondromyxosarcoma	Lost
13311	W	M	34	Jaw lower left	2	Tumor	Osteochondroma	Periosteal new bone bone destruction	Excision (3 times) resection; radium	Chondromyxosarcoma	Recurrence living 7 yr
12943	W	M	48	Femur lower	37	Pain; tumor; pathologic fracture	Osteochondroma		Curettement (2 times); amputation	Chondromyxosarcoma	Dead 3 yr later
12331	N	M	33	Humerus, lower	14	Pain; tumor	Osteochondroma		Excision	Chondromyxosarcoma	Lost
10150	W	F	33	Femur lower left	6	Tumor	Osteochondroma	Granular periosteal new bone rounded exostosis	Excision	Chondromyxosarcoma	Dead 4 yr later
10000	W	M	22	Pelvis	1 & 36	Tumor			Exploration	Chondromyxosarcoma	Dead 1 yr later
9330	W	M	42	Ribs	14	Multiple tumors	Chondromas		Excision	Chondromyxosarcoma	Dead 10 mos. later
8473	N	M	60	Humerus, upper	1	Pain; tumor	Chondroma		Curettement	Chondromyxosarcoma	Dead 4 yr later
8111	W	M	36	Os calcis, right	23	Pain			Excision; amputation	Chondromyxosarcoma	Recurrence dead (?)
6773	W	F	60	Humerus, upper	10	Trauma; pain; tumor	Osteochondroma	Exostosis undergoing destruction	Excision (4 times); amputation	Chondromyxosarcoma	Dead 3 yr after last operation
1972	W	M	51	Femur lower	3	Stiffness; tumor	Chondroma	Translucent periosteal shadow; bone destruction	Amputation	Chondromyxosarcoma	Dead 3 mos. later
906	W	M	70	Humerus	1 & 36	Trauma; pathologic fracture		Periosteal shadow	Amputation	Chondromyxosarcoma	Dead 13 yr later from other causes
745	W	M	67	Jaw lower	3	Pain tumor; extraction of teeth	Osteochondroma	Bone absorption; pathologic fracture	Excision	Chondromyxosarcoma	Well 3 yr., lost
633	W	M	50	Ribs		Four repeated fractures of ribs			Excision	Chondromyxosarcoma	Local recurrence; dead 5 wks. after discharge

TABLE 14. CLINICAL FEATURES OF PRIMARY AND SECONDARY CHONDROSARCOMA

	Primary	Secondary
Number of cases	121	118
Origin	Junction of tendon to bone	Previous benign skeletal tumors
Sex	Males, 2 1	Males, 2 1
Race	Blacks, 15%	Blacks, 6%
Most frequent ages	14 to 21 years	30 to 50 years
Favorite sites	About knee upper end of humerus	Shoulder and pelvic girdle knee and heel
Duration of symptoms	3 to 5 months	2 to 25 years
Usual symptoms	Pain tumor tenderness	Pain tumor tenderness
Trauma	22%	22%
Pathologic fracture	None	6%
Constitutional manifestations	Occasional fever leukocytosis enlargement of regional lymph nodes secondary anemia	Systemic reactions rare secondary anemia
Roentgenograms	Periosteal translucent tumor slight new bone	Central caseous destruction with periosteal reaction
Microscopic features	Pleomorphic forms of cartilage predominate	Myxoma and fetal cartilage predominate
Percentage of 5 yr cures	15%	44%



FIG. 86 (No. 34522) Portion of the specimen from the leg amputated in January 1924. The waxy hyalinized mass represents the malignant portion, the spongy honeycombed area in the condyle, the primary portion of the growth. (See also Fig 83.)



FIG. 87 (No. 34522) Emphthalmos caused by metastases to the frontal bone. The photograph was taken in November 1927 (See also Figure 83.) The patient died in October 1930.

FIG. 88. Roentgenograms of chondrosarcoma arising in an osteochondroma of the tibia.

persists in the roentgenogram and in which the superimposed malignant change is visible as a fuzzy infiltrating periosteal shadow When a previous osteochondroma is implicated, the evidence of this original lesion is usually visible in the form of a nostic feature emphasized by Phemister (see Bibliography Chap 5) Destruction of the cortical bone with invasion of the medullary cavity follows, and pathologic fracture may occur (Figs. 92, 93, 94, and 95)



Fig. 89 (No. 43022) Roentgenogram of a small chondromyxosarcoma embedded within the malleolus of the tibia. The patient gave a history of injury and continued weakness in the left ankle at this point dating back 19 years. The acute symptoms of stiffness and soreness had been present 8 weeks. The lesion was excised and cauterized with 50 per cent zinc chloride The patient has continued well for over 15 years.

widened metaphyseal region in the affected or adjacent bones, and the persistence of the more thoroughly ossified portion of the base or pedicle of the exostoses (Figs. 81, 90 and 91)

In advanced cases, the entire tumor site becomes the seat of an infiltrating granular mass in which scattered elements of splintered osseous material may be seen. This stippling in the soft parts is a diag

The most frequent sources of confusion of the diagnosis of secondary chondromyxosarcoma are benign osteochondromas, myositis ossificans and the sclerosing form of osteogenic sarcoma. The differentiation of this form of chondrosarcoma from a benign exostosis when both are actually present in the same film is sometimes extremely difficult. The most helpful point is the gradual blotting out of the lines of configuration



Fig. 90 (No. 32317) Secondary chondromyxosarcoma arising at the site of an old exostosis in a white man, aged 25 The malignant change occurred 18 months previously as far as can be determined, following a severe blow to the right thigh by an automobile crank. The tumor was explored, and the sections pronounced chondrosarcoma. Amputation was advised, but refused. The patient carried the tumor for 4 years longer at which time there was a pathologic fracture and the tumor had reached such size that the patient consented to amputation, the specimen weighing 72 pounds (32.7 kg.) The patient remained well 2 years after operation, despite a transient hemiplegia which occurred postoperatively Six years after the first examination, however his health began to fail, he became despondent and committed suicide Autopsy was not obtained. The roentgenogram shows the original base of the exostosis and the splintering of bone and spotty calcification typical of secondary chondromyxosarcoma.



Fig. 91 Roentgenogram showing chondrosarcoma, surrounding the fibula, but arising from an osteochondroma attached to the lateral aspect of the metaphysis of the tibia.

of the benign lesion from above inward by the malignant change (Fig 81) When the destructive process affecting the bone reaches the medullary cavity and if pathologic fracture occurs, the diagnosis of malignancy becomes increasingly certain (Fig. 92) In myositis ossificans traumatica in which the lesion has been of relatively short duration and has reached a stationary size, the differential diagnosis is not difficult because of the wedge-shaped configuration of the growth and its dense and laminated



FIG. 92. (No 42888) Roentgenogram showing malignant change in the upper end of the humerus of a patient who had multiple chondromas of the left hand and a benign chondromatous lesion of the upper end of the humerus. The invasion of the marrow cavity and the pathologic fracture indicate a secondary chondrosarcoma The patient, who was 50 years old, said that his left arm had always been more crooked and shorter than the right and that the nodules on the left thumb and forefinger shown in the roentgenogram had been present for over 40 years. None of these tumors bothered him until 2 years previously following a fall on the ice. Since that time the upper part of the left arm had been painful, and the swelling there had increased rapidly A resection of the upper end of the humerus was performed, following which the patient died 18 hours later of postoperative shock.

ructure (Lewis*) But when the myositis ssificans becomes progressive and the leon becomes increasingly dense, shaggy nd large, it is difficult to tell whether the rowth is still benign or whether secondary hondrosarcoma is present (Fig. 96) In uch cases, the lesion is usually malignant, nd the diagnosis should be confirmed by iopsy Sclerosing osteogenic sarcoma is distinguished from this secondary form of chondrosarcoma by the greater density of the periosteal shadow and by the fact that it produces sclerosis of the marrow cavity rather than advanced destruction of cancellous bone.

PATHOLOGY AND HISTOGENESIS

In the histogenesis of this group of secondary chondrosarcomas, there is no difficulty in tracing a relationship between the benign osteochondromas and chondromyxomas and this form of sarcoma of the bone.

Lewis, D: Myositis Ossificans, J.A.M.A. 80 1281, 1923.

The real difficulty arises in attempting to differentiate these malignant lesions pathologically from the benign cartilaginous tumors from which they arise and to recognize them as secondary forms of chondrosarcoma as distinguished from the primary form.

In many cases, at the operation or in the gross specimen the evidence of the original benign growth is plainly visible and will have been inferred from the roentgenogram. This is true in cases in which a benign exostosis, hereditary chondrodysplasia, Paget's osteitis deformans or multiple enchondroma is unquestionably present and the malignancy can be seen as a superimposed change with the more recent and rapid growth surrounding the old and more mature process (Fig. 98) From an analysis of the gross specimen and microscopic sections, it can be concluded that the previous benign cartilaginous growth is only partly responsible for the more recent and more rapidly proliferating chondrosarcoma.

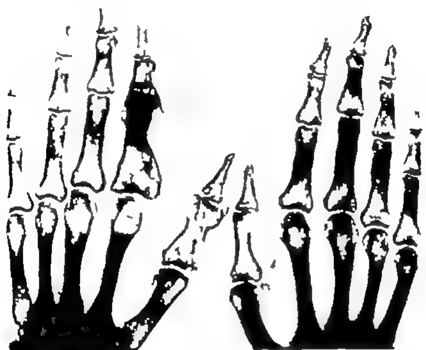


FIG. 93 (No 42888) Roentgenogram of the hands of the patient shown in Figure 92. Note the chondromatous lesions in the left thumb and forefinger

By this is meant that the cartilaginous structure or osteochondral mass built up by the preceding benign growth does not undergo transformation into sarcoma, but acts as a fossil remains which is gradually destroyed by the new malignant growth arising from the primitive connective tissue that always persists at the periphery



FIG. 94. (No 42888) Gross specimen of the resected humerus shown in Figure 92. The cartilaginous tumor has invaded the shaft of the humerus and produced pathologic fracture visible at the site of the cystic area in the gross specimen but shown only poorly in the roentgenogram.

Histologically this is evident in an emphatic way At the site where the sarcoma is arising, there are always a reduplication and proliferation of the connective-tissue elements, which are present only in insignificant proportions in the benign cartilaginous group of tumors and always interspersed with chondral elements in the primary chondrosarcoma. This proliferation of connective tissue in the secondary chondrosarcoma soon takes on a myxomatous character and it is because of the conspicuous amount of this myxomatous proliferation present that Bloodgood originally called attention to them under the term "pure myxoma of bone" (Fig 103)



Fig. 95 Roentgenograms showing a chondrosarcoma arising from an exostosis on the medial border of the scapula. This patient had multiple exostoses and central chondromas. Lateral and posterior views.



Fig. 96. Chondrosarcoma arising f an osteochondroma of the coracoid proc ess. The osteochondroma first gav symptoms in 1928. The patient had shoulder girdle disarticulation in 194 He was living in January 1948, but ha metastases to the chest. The autho have observed four osteochondromas the coracoid process. All of them hav given rise to chondrosarcoma. (*Left* Roentgenogram made in 1930 showin malignant change with erosion of th scapula. (*Right*) Roentgenogram mad in 1943 shortly before the should girdle disarticulation. The chondrosa coma was about the size of an adu head and surrounded the entire should joint.

Aside from the relatively large amounts of this myxomatous tissue seen under the microscope, and the evidence of pre-existing benign growths often found in the gross specimens, secondary chondrosarcoma differs pathologically in no essential way f the primary chondrosarcomas. In mi scopic diagnosis, it is at times difficul distinguish both the primary and secon chondrosarcomas from the closely rel benign osteochondromas and chondron omas.* The more densely cellular and al dant character of the connective-ti strands, the interspersion of malig round cells near these strands where border on myxomatous tissue, and the pearance of large multinucleated carti cells with mitotic figures amid the chon lobules, which will be found in the sect of both primary and secondary chondr coma, are absent in benign cartilagi lesions.

PROGNOSIS AND TREATMENT

When a malignant change has occu in secondary chondrosarcoma, the dur

* The reader is referred to the chapters o teochondromas and chondromas or chondro mas, microscopic features (Chaps. 2, 3 and



FIG. 97 (A) (No 27299) is a roentgenogram of a typical benign case of myositis ossificans (B) (No 27702) shows a progressive and invasive case of myositis ossificans in which malignant change is to be suspected.



FIG. 98. (No. 39952) Illustrations showing malignant change in a benign exostosis in a Negro boy *aged 18 following an injury two and one-half years* previously This photograph of the patient, taken in June 1929 shows the bony swelling at the site of the adductor tubercle, 18 months after the onset of malignant change.

of life varies from 2 to 10 years. There may be one or more recurrences. In all probability the first recurrence in some of these was a benign growth, the malignant change following the recurrence These secondary malignant tumors grow more slowly than primary chondrosarcoma and are probably influenced in this matter by the advanced age of the person. If such a tumor is explored and the microscopic section only is submitted for pathologic analysis and prognosis, it is practically impossible to render an accurate opinion because of the gradual gradation from the benign chondromas, on the one hand, and the close resemblance to primary chondrosarcoma, on the other If a roentgen film is available however the chances of a cure can be largely estimated by the amount of bone destruction and the extent of the invasion of the marrow cavity by the tumor The greater the degree of medullary involvement, the worse is the prognosis.



FIG. 99 (No 39952) Roentgenogram taken in December 1927 showing the early signs of malignant change in the exostosis. Note the fracture through the benign portion of the lesion and the sarcomatous periosteal reaction on the opposite side of the femur (See also Fig 98.)



FIG. 100 (No. 39952) Roentgenogram showing the progress of the sarcomatous growth in June 1929 (See also Fig. 98.)

The percentages of five year survival in this form of tumor is 44 (Table 15) Of the 38 patients living and well more than five years after treatment, the majority were treated by radical resection or amputation. In the other cases, excision or curetting followed by cauterization with the soldering iron and subsequent deep roentgen therapy or radium treatment accomplished a cure In one of the cases in which a radical

resection of the jaw was done after several recurrences following excision, radium was used following the resection tion In two other cases there were numerous recurrences prior to the amputation or radical resection.



FIG. 101 (No 39952) Gross specimen showing a secondary chondromyxosarcoma arising from the periphery of a benign pedicle exostosis in a Negro boy aged 18 Symptoms referable to the original exostosis had been present for over three years. The patient committed suicide three years after amputation of the limb Note that the fibrocartilaginous sarcoma mass not only extends around the dark pedicle of the exostosis but that it is also present in the bulb or cartilaginous cap of the previously benign growth (See also Fig. 98.)

The remarkable feature in these cases of cure is the occasional effectiveness of radium or cauterization and the number of recurrences due to ineffective treatment before ultimate recovery was achieved. In one case which must be looked on as a cure of five years duration, amputation was performed four years after the original exploration

All the patients who were cured except three were over 25 years of age, in three the tumor was at the upper end of the humerus, and in two it extended above the midshaft of the femur Cures in the upper portion of the humerus or femur speak for low-grade malignancy in this type of tumor since they are extremely rare in this loca-

TABLE II RESULTS OF TREATMENT IN CASES OF SECONDARY CHONDROSARCOMA

Total number of cases followed	107
Number of cases well less than five years	21
Total number of fatal cases	48
Number of patients living over five years	38
Percentage of five year survivals	44%

tion when the growth is primarily malignant. The actual role of the incomplete operation cannot be estimated in any of these cases, since it is possible that the original unsuccessful operations were performed on a benign tumor and a malignant change followed at a later date, closely preceding a cure. If biopsy is performed and not followed by immediate amputation, cauterization and irradiation are advised, because of the danger of transplanting tumor in the wound. Following competent pathologic consultation radical surgery should then be instituted.



FIG. 102. (No. 39952) Photomicrograph taken from the margin of the malignant growth, showing the sarcomatous proliferation of connective tissue

the final operative procedure. Unfortunately exact microscopic studies on the tissue from each operation are not at hand to settle this point. However in view of the many cases that have ultimately proved fatal after recurrences following incomplete operation, it is only fair to assume that radical operation is usually necessary at the outset of the malignant course to effect

In deciding on the operative procedure it is well to bear in mind the fact that irradiation is not usually effective in this form of sarcoma. Only when complete eradication of the tumor cannot be accomplished by radical resection or amputation does irradiation present advantages. However if the tumor is cartilaginous and its benign or malignant nature is in doubt, it

is best to excise with the cautery and follow with deep roentgen therapy * Implantation of radium or radon in bone, however is to be avoided.

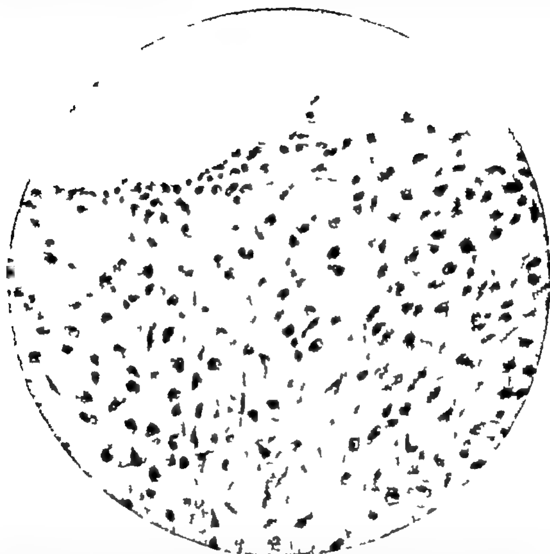


Fig. 103 (No 6773) Microscopic structure of the lesion shown in Figure 81 This portion of the tumor is composed entirely of embryonic precartilaginous connective tissue and fetal cartilage cells, embedded in a hyaline matrix. This is a so-called pure myxoma of bone of Bloodgood.

SUMMARY

Secondary chondromyxosarcomas may complicate a benign exostosis, a benign chondroma, or benign multiple skeletal diseases such as Paget's osteitis deformans or hereditary deforming chondrodysplasia. Most often the patients are between the ages of 35 and 55 but occasionally a person under 30 is affected. The location differs from the primary form of chondrosarcoma in that there is a greater tendency for the regions about the upper humerus, ribs and heel to be involved. The total duration of

* Dr W Sampson Handley of London, in a personal communication (Feb. 1 1931) reviewed his experience with radium in sarcoma of this type originally reported in, Cancer Conference—London—William Wood & Company 1928 p. 377 He chisels away the main tumor after which large doses of radium are buried for a short time in the wound (500 mg. enclosed in 1 mm. of platinum for 24 hours) Of five patients thus treated one is well for three years and two had recurrences after three years of active life with freedom from pain. The results are not sufficiently favorable to risk the danger of osteomyelitis with such irradiation

symptoms averages over six years, the more recent and acute symptoms following upon a history of rheumatic pain for many years in the region of an osteochondroma or some permanent defect such as a crooked or a short limb Although the actual onset of malignancy is difficult to establish, this change does not precede the onset of the acute symptoms by many months.

In the roentgenogram the most easily recognized secondary chondrosarcoma is that in which distinct evidence of the nature of the primary lesion persists in the roentgenogram, and in which the superimposed malignant change is visible as a fuzzy infiltrating periosteal shadow When a previous osteochondroma is implicated, the evidence of this original lesion may remain in the form of a widened metaphyseal region, or the more thoroughly ossified portion of the base or pedicle of the exostosis may persist. In advanced cases the entire tumor site becomes the seat of an infiltrating granular mass in which scattered elements of broken osseous material may be seen. Destruction of the cortical bone with invasion of the medullary cavity follows and pathologic fracture may occur

Histologically the malignant change giving rise to secondary chondromyxosarcoma bears out the connective-tissue origin of this neoplasm. At the site where the sarcoma is arising there is, first, a proliferation of the precartilaginous connective-tissue elements, which are present only in insignificant proportions in the benign cartil inous group and always interspersed w chondral elements in the primary chond sarcoma. This proliferation has a myxom tous character and therefore Bloodgo originally called attention to it under t term "pure myxoma of bone."

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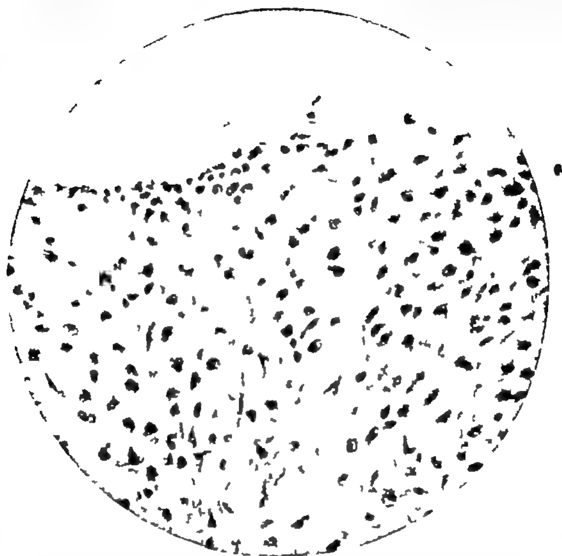


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Postoperative five-year survivals in the secondary form of chondromyxosarcoma average about 44 per cent. Radical resection or amputation is the treatment of choice. Failing this, radical excision followed by external irradiation should be undertaken. The disease runs a chronic course even in fatal cases, some patients succumbing only after five to ten recurrences over a period of from six to eight years.

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7

Chondroblastic Tumors: Benign and Malignant

In 1930 and 1931 the authors called attention to the roentgenologic and pathologic features of chondroblastic tumors of the epiphyseal line. These are vascular cartilaginous tumors which occur in young adults, usually on the metaphaseal side of the epiphyseal line. They produce destruction in the cancellous spaces and an overlying periosteal reaction. In the early descriptions of this tumor an occasional case was classed as a cartilaginous growth. Borst illustrated a microscopic picture of such a tumor under the heading of chondrosarcoma, and Kolodny cited a similar case as osteogenic sarcoma. Because of the proliferation of giant cells about vascular spaces at the margin of these growths and the islands of cartilage that have undergone calcification, another school classified these growths as variants of giant-cell tumors. Bloodgood looked upon them as malignant variants of giant-cell tumor. Ewing published a case as a metastisizing giant-cell tumor and described others as benign calcifying giant-cell tumors. Later Codman published a group of cases as epiphyseal chondromatous giant-cell tumors.

In the early editions of this work, the authors first pointed out that these were epiphyseal line tumors and that the proliferating tissue was chondroblastic rather than composed of giant cells. It was also pointed out that some of these cases died of metastases in spite of amputation whereas others followed for over five years were well following curettage and irradiation. In 1942 Jaffe and Lichtenstein agreed with the authors as to the cartilaginous origin of these growths and proposed the term "benign chondroblastoma of bone" for them. A restudy and careful follow up of a series of these patients indicates that these growths may be either benign or malignant and that a careful microscopic study will distinguish between these two forms.

CLINICAL FEATURES

These tumors occur before the ossification of the epiphyseal line is complete. In our series of cases, the age limits were between 10 and 24 years. In the series of cases reported by Jaffe and Lichtenstein in 1942, the age distribution was from 13 to 17 years. The location of these growths is predominantly in the ends of the long bones about the knee joint (the upper tibia and lower femur) and in the upper humerus. The bulk of the tumor is on the shaft side of the epiphyseal line, but the epiphysis is also invaded, and the growth may be confined to the epiphysis in some cases. The duration of symptoms varies from 1 to 16 months in our cases, and from 3 to 12 months in those of other authors. The sequence of events in the clinical history is not distinctive. Pain, tenderness and swelling followed by lameness in the affected member are characteristic of the lesion when it occurs in a weight

bearing extremity In two of our patients in whom the tumor was in the lower end of the femur there was effusion in the knee joint, suggesting the clinical diagnosis of tuberculosis.

There is a definite correlation between age and duration of symptoms in this tumor In patients under 20 the average duration of symptoms is less than five months, while in the rare cases in which the patients are 20 years and over the disease averages over three years. The sequence and character of the clinical events are much alike at all ages, and in this respect the history resembles that of primary sarcoma of bone. Trauma, pain tenderness and tumor are reported in the order given in most cases. Lameness is almost a constant accompaniment when the lesion is in the weight bearing extremity Pathologic fracture is reported in only three instances of the series, although this is clearly a bone-destructive neoplasm (the rarity of this complication being attributable in all probability to the acuteness of the disease) Fever leukocytosis and enlargement of the regional lymph nodes are infrequent in this tumor They may be encountered in cases of other types of sarcomas of the bone This detracts from the diagnostic value of these findings, which have frequently been stressed as peculiar to Ewing's sarcoma of the bone (Ewing, Connor) These systemic reactions, as pointed out in a previous study (Copeland and Geschickter) are associated with the rapid growth of the tumor resulting in early dissemination. They are not peculiar to the histologic nature of the growth.

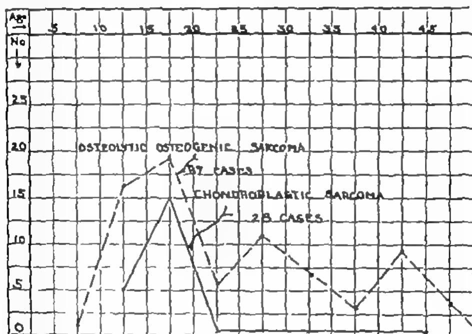


CHART 6 Age incidence in chondroblastic sarcoma (solid line) and osteolytic, osteogenic sarcoma (broken line)

ROENTGENOGRAPHIC FEATURES

The roentgenologic features of these tumors are fairly distinctive They produce rarefaction in the cancellous bone extend on either side of the epiphyseal line and provoke an overlying periosteal reaction usually along a single margin of the bone. This extension across the epiphyseal line and the periosteal reaction occur in the early stage of the growth before marked destruction of cancellous and cortical bone has taken place In the roentgenogram, therefore these tumors differ from benign giant cell tumors in that they in-

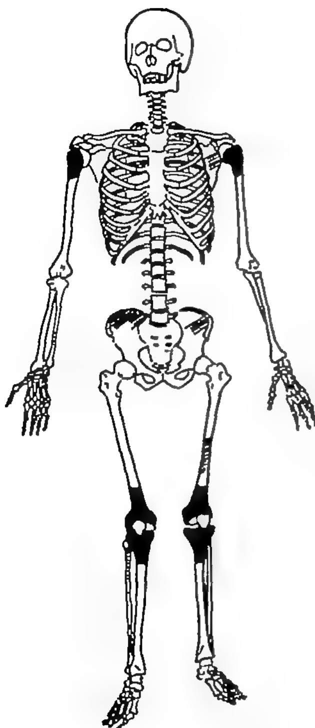


FIG 104 Skeletal distribution of chondroblastic tumors. The black areas are the most frequent sites, and the diagonal lines those less commonly involved.

volve both the epiphysis and the shaft of the bone. They are not rarely confined to the epiphysis. They do not expand beneath a shell of cortical bone nor do they have the coarse trabeculae seen in giant cell tumors. The periosteal reaction also distinguishes them from benign giant-cell tumor

These growths can be differentiated from Ewing's sarcoma in the roentgenogram by the extension into the epiphysis early in the disease, and by the fact that the periosteal involvement extends only along one side of the bone as a rule. There is no cortical thickening The right-angle new bone formation or groomed whiskers of osteogenic sarcoma is lacking The age distribution of this tumor is also helpful in the diagnosis. The occurrence in adolescents distinguishes these growths from benign giant-cell tumor which practically always occurs in the long bones after the age of twenty-one.

Both lesions may cause central destruction and involve an epiphysis of the long bone, but there are definite points of distinction The giant-cell tumor usually occurs in persons over 20, is confined largely to the epiphysis, is coarsely trabeculated in structure and produces little or no periosteal reaction even when perforating its bone shell. Chondroblastomas usually occur in patients under 20, extend on both sides of the epiphyseal line definitely invading the shaft, are multilocular and are always accompanied by a definite periosteal reaction (Figs. 107 and 108) When the earliest stages of this growth are seen in the roentgenogram, the tumor is usually found to be primary in the metaphysis, suggesting sarcoma. From here it extends to involve the epiphysis in most cases but rarely invades the bone in the opposite direction. (Fig 107) This peculiarity in the inception of the tumor indicates how intimately it is connected with the growth zones of the long bones, which, as is well known, are on the metaphyseal sides of the epiphyseal lines.

While the tumor is predominantly central in location, there is usually an escape beyond the cortex into the subperiosteal region, particularly near the epiphyseal line. In such instances the periosteum is raised by a translucent shadow and bone forma

tion from the inner side of the periosteum is noticeably lacking.

The age distribution of this tumor aids in distinguishing it from a solitary focus of metastatic carcinoma. In cancerous deposits that are secondary in the bone the locali zation of the involved area is usually nearer source of confusion. There is a similarity in the age of the patient, in the acuteness of the symptoms and in the tendency to involve the long bones. However in Ewing's sarcoma there is more formation of new bone, a more diffuse involvement of the shaft with an extension to the midshaft re-



FIG. 105. (No. 26792) Roentgenogram of a benign chondroblastic tumor extending on both sides of the epiphyseal line. The lesion shows the typical multilocular structure of a chondromatus growth and the periosteal reaction suggests malignant character. This patient was treated by radium treatments following a curettement. He is well 20 years later.

to the midshaft region. The type of periosteal reaction seen in chondroblastic tumors and the multilocular subcortical shadows are practically always absent. Also the involvement of the lower end of the femur upper end of the tibia and lower end of the radius is rare in metastatic carcinoma while frequent in this tumor.

Ewing's tumor may occasionally be a gion, and the involvement of the epiphysis so characteristic of chondroblastomas is never seen in early cases.

GROSS PATHOLOGY

At operation, the tumor may be found extending into the soft parts covered by a *thin envelope of fibrous tissue*, invading the subperiosteal regions covered by an in-

tact periosteum or entirely within a bone shell. Most of the neoplasm is usually within the medullary cavity or within cancellous bone The tumor tissue itself varies in consistency according to the degree of vascularity and necrosis. Often it has the appearance of organized hemorrhage, being dark red or jellylike in appearance and contains scattered bits of necrotic bone At other times, it is firmer gray or bluish white in color with translucent areas resembling hyaline cartilage. Small cystic cavities may be seen.

The mode of extension of the tumor is interesting. In some specimens in which the limb has been amputated, the unossified epiphyseal line can be clearly traced except at the point where there is proliferation of tumor (Fig 110) Here it is substituted by a hemorrhagic and necrotic mass which extends in irregular fashion into the metaphyseal region of the cancellous bone, stimulating very little reaction The tumor evidently does not disseminate as readily within the cancellous bone as it does in the subperiosteal spaces. Once it has reached these spaces the medullary foci of tumor growth are joined by a large, proliferating, subperiosteal mass.

The most important information disclosed by the examination of the gross specimens is the continuity between the tumor mass and the unossified epiphyseal line. The epiphyseal cartilage forms a plane of origin for the new growth, for whether the foci of invasion of the tumor extend into the metaphysis or into the epiphysis or laterally into the subperiosteal zone a connection is always demonstrable between the area in which the epiphyseal cartilage is destroyed and the masses of tumor substance, provided the growth is not too far advanced.

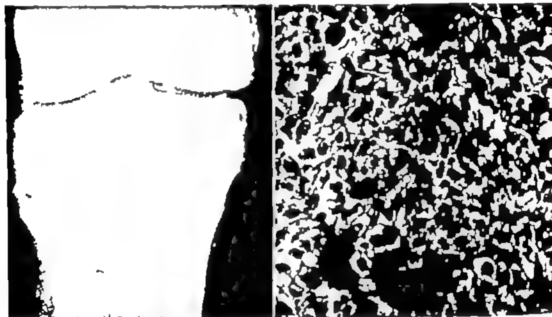


FIG. 108 (No 56324) Roentgenogram and photomicrograph of a chondroblastic tumor in the upper tibia. (*Left*) Roentgenogram shows that the lesion is about to perforate the bony shell on the medial aspect of the tibia, where it has provoked a faint periosteal reaction. (*Right*) Photomicrographs show the pleomorphic character of the chondroblasts and beginning calcification.

The tumor tissue found on exploration of these growths is often indistinguishable from the hemorrhagic grumous material found in giant-cell tumor the hyaline material in chondromas or in so-called malignant aneurysms of the bone (Fig 111) Occasional zones of cartilaginous material in an otherwise necrotic and hemorrhagic mass

or the connection of the tumor tissue with a persisting unossified epiphyseal line should always arouse suspicion of chondroblastoma. Syrupy jellylike masses of translucent chondromyxomatous material and cystic degeneration seen in chondromyxosarcoma are not characteristic of this neoplasm but may be present to a limited extent.

MICROSCOPIC FEATURES

Under the microscope chondroblastic tumors are composed of a mass of young and adult cartilage cells undergoing calcification. The tissue, although distinctly of the hyaline cartilage variety as is indicated by the intercellular substance or matrix, differs from normal cartilage in the vascularity and paucity of the intercellular material (Fig. 112) Strands of precartilaginous connective tissue with myxomatous and early fetal cartilage cells are absent. The absence of these cells, along with the vascularity distinguishes this tumor under the microscope from the primary and secondary forms of chondromyxosarcoma discussed elsewhere New bone of tumor origin which may be sparsely present in chondromyxosarcoma is absent in these growths. The tumor never passes beyond the stage of calcification—another important distinguishing microscopic feature This is verified by a study of the metastatic pulmonary nodules. Although reactive new bone may be present at the periosteal margins of chondroblastic tumors, it is not found in metastases (Figs. 113 114)

On examination with the high power the predominant elements are polyhedral and angular cells with prominent nuclei and ill defined cytoplasm. The younger cells have small, dark nuclei with a crowded chromatin substance while in the older cells the nuclei are larger and more vesicular with a distinct central nucleolus and a definite nuclear wall. Many of the cells have a scanty or ill defined cytoplasm, but in others there is a prolongation of cytoplasmic processes and within the meshwork of this reticulation a clear faintly staining intercellular substance is often observed (Fig 116) This represents an attempt at the formation of typical cartilaginous areolae prior to the stage of calcification.

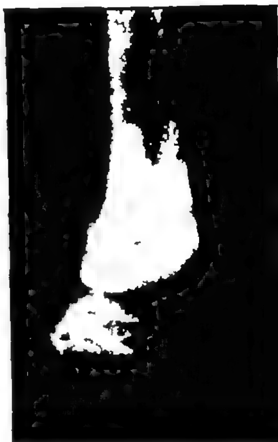


Fig. 107 (No 35226) Roentgenogram of a chondroblastic sarcoma arising at the epiphyseal line and extending for some distance into the metaphysis. Note the small focus of osseous destruction in the epiphysis and the elongated area of rarefaction extending toward the shaft. This lesion proved fatal, and the patient died six months after the onset of the symptoms, in spite of amputation

A characteristic histologic feature of these neoplasms is the intercellular latticework formed by the calcifying matrix. This latticework pervades the tumor with sketchy fragmentary curved lines, emphasized by varying degrees of calcium deposition. Here and there larger areas of uncalcified matrix appear which are easily recognized as typical hyaline cartilage, and in isolated por



FIG. 108 (No 61936) Roentgenogram of benign chondroblastic tumor of the lower femur The patient is well nine years following amputation. The lesion has two foci of bone rarefaction, at the epiphyseal line in the lower femur and just above in the shaft. Note the periosteal reaction in the anteroposterior view This lesion is nearly identical with that shown in Figure 107 (No 35226) The former patient is living, while the latter is dead.

tions of the tumor circumscribed islands of chondroblasts may give the tumor an alveolar appearance. The tumor is extremely vascular with many blood spaces enclosed by a single layer of endothelium. Near these vascularized areas, and usually toward the periosteal margin of the growth, giant cell osteoclasts are numerous. These giant cells are of the epulis type, and sections cut from the margins of these growths may closely simulate a benign giant cell tumor and have led in several instances to an erroneous diagnosis.

There are two important aspects to the microscopic interpretation of chondroblastic tumors. The first is the distinction of these growths from benign giant-cell tumors. The second is the differentiation of chondroblastomas into benign and malignant forms. The presence of chondroblasts and the hyaline matrix, with or without a web of calcification traversing the hyaline material, differentiates these neoplasms from benign giant-cell tumors.

The division of chondroblastoma into benign and malignant forms by microscopic study is a more difficult task. It must be remembered that in the roentgenograms the majority of these growths give rise to a periosteal reaction, suggesting an osteogenic sarcoma. It is tragic to recommend a radical procedure if the tumor is benign and equally tragic to forego such treatment if the tumor is malignant. We have re-

studied our cases and through the follow up reports have divided the sections into two groups—those remaining well following therapy and those known to have died of the disease The contrasting features of benign and malignant growths are shown in Figures 112 and 115 In the *benign* growths, the nuclei of the chondroblasts are uniformly small. The cytoplasm is moderate in amount, stains faintly and is ill-defined in its margins. The hyaline matrix is moderate in amount, but infiltrates in fine strands, with well-defined reticular fibers. Calcification is usually confined to this matrix. In the malignant growth, the nuclei of the chondroblasts are frequently of large size, bizarre in shape and variable in their staining reactions. Mitotic figures are frequent. The calcification is not confined to the matrix but overlaps the cellular elements, unless the section is cut with extreme thinness.

Margins of the tumor may show solid islands of chondroblasts arranged in a somewhat alveolar fashion infiltrating fibrous tissue Much of the tumor is composed of such alveolar masses with little or no hyaline matrix.



FIG. 109 (No. 27309) A chondroblastic sarcoma suggesting in the roentgenogram a Ewing's tumor The lesion extends shaftward away from the epiphyseal line but definitely involves the epiphysis. There is a periosteal reaction resembling onion peel formation and slight sclerosis with widening of the shaft suggesting a Ewing's sarcoma. The small focus of epiphyseal involvement is rare in Ewing's sarcoma. This case proved fatal within a year despite a disarticulation at the hip joint. For the microscopic picture see Figure 114 (A) and (B) were taken before curettement. (C) was taken one week later

HISTOGENESIS

The age incidence of this tumor its location at an active epiphyseal line and the easy identification of the proliferating cartilage cells as chondroblasts similar in type to those present in the skeleton of the embryo immediately after the long bones have been preformed in cartilage supply the clues necessary to an analysis of the histogenesis (Fig. 117)

In the adolescent period in normal persons, there is, at the epiphyseal lines of the upper end of the humerus, the lower end of the femur upper end of the tibia and lower

end of the radius where these tumors predominate, a final spurt of growth in the length of the appendicular skeleton previ ous to the obliteration of the growth disks



Fig 110 (No. 35226) A longitudinal section of the amputated specimen of the chondroblastic sarcoma shown in Figure 107 The tumor had fungated through the operative wound made by two curettements. The relation of the tumor mass to the unossified epiphyseal line is clearly discernible Note the dark hemorrhagic character of the tissue.



Fig. 111 (No. 23473) A longitudinal section through the amputated specimen of a chondroblastic sarcoma involv ing the upper end of the humerus of a white girl, aged 9 The mass of tumor tissue has obliterated the metaphyseal region of the upper end of the humerus and partially invaded the epiphysis. A pathologic fracture has occurred through the vascular area. The upper part of the tumor is of cartilaginous consistency This patient died four months after the amputation.

This spurt in development in the long bones takes place on the metaphyseal side of the epiphyseal line and is accomplished by a twofold process. There is a reproduction of cartilage cells in the form of chondroblastic proliferation, and, in addition to this reproduction there are maturation and further development of the cartilage cells terminating in calcification. Later vascular ization with resorption of the calcified ma terial takes place and this is followed by the substitution of permanent new bone. In this final process of substitution, brought about by new blood vessels and the resorptive power of giant-cell osteoclasts, the car tilage cells play no active role, but constitute in their calcified state a necessary stim-

ulus to final ossification This entire process which normally is gradual and orderly is distorted and hurried by the etiologic factors that precipitate the new growth.

This new growth coincides at its inception with the normal developmental process at the epiphyseal line but departs from the normal in that an earlier phase of cell proliferation persists, resulting in a preponderance of chondroblastic growth and calcification.

The result of this distortion is a tumor characterized by rapidly proliferating chondroblasts that abort into an end stage of calcified cartilage without producing, except in a fragmentary way the usual hyaline matrix typical of normal adult cartilage. Apparently while still in a proliferating stage many chondroblasts are ensnared in a calcifying matrix of their own making and are petrified.



Fig. 112. (No. 35226) Photomicrograph of a section taken from the tumor shown in Figures 107 and 111 The section shows the proliferation of chondroblasts with a small amount of calcified cartilage Vascularization and giant cell proliferation were marked in this case and originally led to an erroneous diagnosis of giant-cell tumor

The vascularity of the tumor and the giant cell areas are secondary features. Giant-cell invasion followed by vascular



FIG. 113. (No 32348) Calcifying metastatic pulmonary nodule in chondroblastic sarcoma. The photomicrograph shows the end-stage of the tumor process. Calcification but not new bone is produced. The patient was a white girl, aged 16 who died four months after the onset of symptoms.

channels in the normal order of osteogenesis in the long bones.* Apparently in this tu mor the invasion of the calcified structures by giant cells and blood capillaries may be a normal defensive response on the part of the adjacent periosteum. This is indicated by the fact that such areas are always more pronounced at the margin of the tumor and are notably lacking in metastatic pulmonary nodules where an end stage of unresorbed deposits of calcium is the rule (Figs. 113 and 114) Some vascularity (mainly vessels of the thin endothelial wall type) however

* Geschickter C. F., and Copeland, M. M Osteitis fibrosa and giant-cell tumor Arch. Surg. 19: 169 1929



FIG. 114 (No. 27509) Photomicrograph of the tumor shown in Figure 109 Giant-cell invasion of an area of the tumor undergoing calcification is taking place. The section was taken from the margin of the tumor This patient died nine months after treatment.

must be looked on as a feature common to rapidly growing tumors in general.* The presence of these vascular foci with giant cells accounts for the frequent mistakes by competent pathologists in diagnosing these neoplasms benign giant-cell tumor meta

* This view that the giant-cell areas in chondroblastic tumors are a product of normal reacting bone it is believed, is nearer the truth than the supposition that they are a further stage in the osteogenesis of cartilaginous bone by the chondroblasts. Since the death of the chondroblasts with the formation of the calcified matrix can be observed under the microscope it is difficult to see how they could survive to initiate the giant cell phase. The fact that giant cells are more numerous at the margin of the tumor at the site of normal reactive bone supports this view

TABLE 16 CHONDROBLASTOMAS

Path. No.	Race, Sex and Age	Location	Duration, mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Results of Treatment
62154	W M 15	Humerus, upper	11	Pain, tumor	Rarefaction at epiphyseal line extends in epiphysis	Biopsy, irradiation	Proliferating chondroblasts	Well 7 yr
61934	W M 17	Femur, lower	11	Pain, tumor	Rarefaction, cortical thinning, periosteal reaction	Biopsy, irradiation	Proliferating chondroblasts	Well 7 yr
61092	W M 16	Tibia, upper	3	Trauma, pain	Rarefaction of epiphyseal line, periosteal reaction	Curettage 1940, amputation 1941	Proliferating chondroblast	Well 7 yr
60768	W M 18	Humerus, upper	3	Pain, tumor	Rarefaction at epiphyseal line	Biopsy, irradiation, resection	Proliferating chondroblasts	Well 9 yr
58448	W M 10	Tibia, lower	1½	Trauma, pain	Rarefaction at epiphyseal line, periosteal reaction	Biopsy, irradiation	Malignant chondroblasts, calcification	Dead 2 yr later
44958	W M 18	Femur, lower	12	Pain, joint swelling	Bone rarefaction	Curettement, irradiation	Proliferating chondroblast	Well 16 yr
44090	W F 24	Humerus, upper	6	Pain, tumor	Bone rarefaction	Curettement	Proliferating chondroblasts	Unimproved
40672	W M 19	Tibia, upper	4	Tumor, pain	Central rarefied area, periosteal roughening	Curetted twice, irradiation, amputation	Proliferating chondroblasts, giant cells	Dead 3 yr
40429	W M 10	Femur, shaft		Pain, tumor	Expansion of shaft by non-radiating new bone, area of central destruction	Exploration, curetted	Proliferating chondroblasts, Calcification, giant cells	Dead 5 mos. later, autopsy
39756	W M 15	Humerus, upper	11	Trauma, pain, tumor	Central rarefied area	Curetted	Proliferating chondroblasts, Calcification, giant cell	Well 14 yr later
39484	W F 15	Scapula, neck	6	Pain, tumor	Central rarefied area	Curetted	Proliferating chondroblasts, Calcification, giant cells	Living 3 yr
38432	W F 20	Femur, shaft	12	Pain, tumor	Central rarefied area, soft part shadow	Curetted, toxins	Proliferating chondroblasts, Calcification, giant cells	Dead 9 mos. later
37882	W F 14	Femur, lower	2	Pain, limp	Subcortical rarefied area, soft part shadow	Amputation	Proliferating chondroblasts, Calcification	Dead 21 mos. later
37670	W M 20	Tibia, upper		Tumor	Subcortical rarefied area, soft part shadow	Amputation	Proliferating chondroblast, Calcification, giant cells	Dead 21 mos. later
36298	W M 18	Tibia, upper	2	Pain at [illegible]	Central rarefied area	Irradiation, amputation	Proliferating chondroblasts, Calcification, giant cells	Dead 5 mos. later
34826	W M 16	Femur, lower	1	Trauma, pain, tumor	Central rarefied area, periosteal roughening	Curetted twice, amputation	Proliferating chondroblasts, Calcification, giant cells	Dead 6 mos. later
33007	W M 15	Fibula, upper		Tumor		Excision, radium, amputation	Proliferating chondroblasts, Calcification	Dead 6 mos. later
32348	W F 16	Tibia, upper	3	Trauma, pain	Rarefied area, periosteal roughening, soft part shadow	Irradiation	Proliferating chondroblasts	Dead 1 mo. later, autopsy
30163	W F 18	Femur, lower	2	Trauma, pain, tumor	Subcortical rarefied area	Amputation	Proliferating chondroblasts, Calcification	Dead 12 mos. later
29770	W F 30	Radius, lower	2	Pain	Rarefied area with periosteal reaction	Curettement, roentgen treatment, amputation	Proliferating chondroblasts	Well 8 yr
28861	W M 10	Femur, lower	5	Pain, limp, tumor	Subcortical rarefied area, periosteal roughening	Curetted, amputation	Proliferating chondroblasts, Calcification, giant cells	Dead 7 mos. later
28590	W M 11	Humerus, upper	15	Pain, swelling	Rarefied area with periosteal reaction	Curettement	Proliferating chondroblast	Well 4 yr, lost from observation
27809	W F 20	Femur, lower	2	Pain, tumor	Subcortical rarefied area, soft part shadow	Amputation	Proliferating chondroblast, Calcification, giant cells	Dead 8 mos. later
26792	W M 16	Humerus, upper	16	Trauma, pain	Central area of osseous destruction, periosteal roughening	Curetted, radium, toxins, irradiation	Proliferating chondroblast, Calcified cartilage, giant cells	Well 20 yr
22473	W F 9	Humerus, upper	5	Pain, tumor, pathologic fracture	Central area of osseous destruction, periosteal roughening	Amputation	Proliferating chondroblasts, Calcified cartilage, giant cells	Dead 4 yr later
9097	W F 10	Humerus, upper	2	Trauma, pain, tumor	Central osseous destruction, soft part shadow (from gross specimen)	Amputation	Proliferating chondroblast, Calcified cartilage	Dead 3 mos. later

static giant-cell tumor and angiosarcoma. The classification by Codman of these tumors as benign epiphyseal chondromatous giant-cell tumors peculiar to the upper end of the humerus is not supported by the present study In the first place, we find a wider distribution for these lesions, and proved instances of death with pulmonary metastases, in spite of radical operation. Secondly the cartilage present cannot be considered as a passive structure, representing a persistence of the normal unossified epiphyseal line. The chondral elements are actively proliferating and the chondroblasts have definite invasive powers. These chondroblasts and their transitional forms are not characteristic of the normal epiphysis, but resemble the cells seen in the embryo when the skeleton is being preformed in rapidly growing cartilage

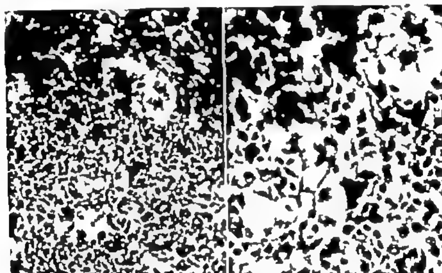


FIG. 115 Low and high-power photomicrographs of a fatal chondroblastic tumor Note the mitotic figures and pleomorphism among the chondroblasts.

PROGNOSIS AND TREATMENT

The most important aspect in the treatment is the division of the chondroblastic tumors into the benign and malignant forms, on the basis of microscopic studies. Since this is an exceedingly difficult task, and since cures have followed curettage, or curettage plus irradiation in the benign forms, it is important that radical operations should be postponed until the sections have been reviewed by competent pathologists. Biopsy followed by roentgen therapy should be the initial procedure in these growths. The section should then be submitted to competent pathologists for final diagnosis. Resection or amputation should not be performed unless the malignant nature of the lesion has been verified.

Chondroblastic tumors are a new clinical entity as far as the modern literature is concerned. Very few cases have been separated from the categories of chondrosarcoma and atypical giant-cell tumors. To date, the only series available for review are the cases studied by the authors, those of Codman, of Jaffe and Lichenstein and of Coley and Santora. The authors are the only ones who have followed more than five years a significant series of cases. In our series, the benign and malignant forms are almost equal in number (Table 16.) The 15 malignant cases are usually dead within a period of 9 to 18 months. Among the 10 benign cases followed, there are some patients who have survived from 10 to 20 years.

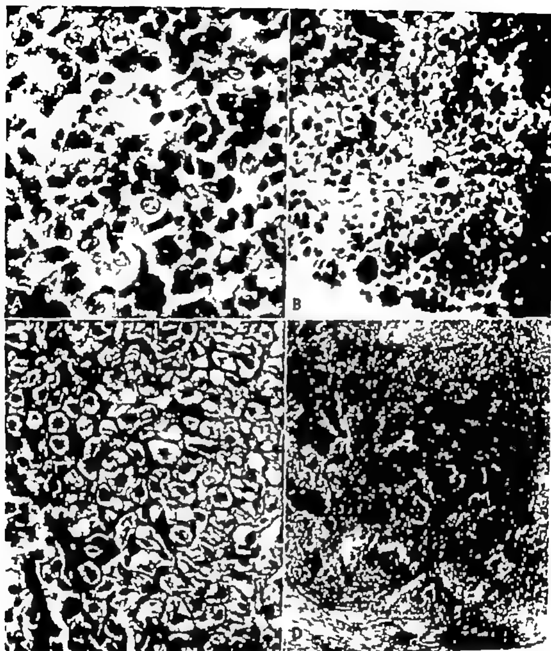


Fig. 116 Microscopic studies of the histogenetic cycle of chondroblastic tumors. (A) showing the proliferation of chondroblasts with clear acidophilic cytoplasm surrounding nuclei of various sizes, represents the earliest stage. In (B) a small amount of the matrix composed of hyaline cartilage is being formed. At (C) the cartilage is undergoing rapid calcification. At (D) the periosteal margin of the tumor is shown. The periosteum is reacting with a slight amount of new bone formation, and the tumor is being invaded by giant cells which in all probability represent a defensive reaction against the calcifying tumor mass.



FIG. 117 Comparison of the neoplastic chondral tissue in chondroblastic tumors with the cartilaginous skeleton of the embryo. (A) shows chondroblastic proliferation in the human embryo and (B) early calcifying cartilage in the same embryo (C) shows chondroblastic proliferation in the chondroblastic sarcoma and (D) early calcifying cartilage in the same tumor These photographs indicate quite emphatically that the neoplastic process concerns the proliferation of chondral elements, and that the giant-cell areas often seen in the sections are a secondary phenomenon.

SUMMARY

Chondroblastic tumors arise from a proliferation of cartilage at the epiphyseal line during the age of puberty and are extremely rare. The tumor occurs most frequently in adolescence, in the region of the epiphyseal line in the upper end of the tibia, the lower end of the femur and the upper end of the humerus. In the roentgenogram there is a mottled area of bone destruction with or without a slightly expanded bone shell and, in addition, a definite periosteal reaction. Under the microscope these lesions show a proliferation of chondroblasts which produce abortive fragments of calcifying cartilage At the margin of these tumors, as a defensive reaction giant cells proliferate and attempt to remove calcified products of the tumor

It is important in microscopic diagnosis to distinguish benign chondroblastic tumors from the malignant chondroblastomas. Patients with benign chondroblastic tumors are well following curettage or deep roentgen therapy Chondroblastic sarcoma, on the other hand, warrants radical resection or amputation, depending on the site of the tumor Radical therapy should not be undertaken without submitting the sections for review by a pathologist specializing in bone diseases.

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8

Osteogenic Sarcoma—The Sclerosing Form of Osteogenic Sarcoma

CLINICAL FEATURES
ROENTGENOGRAPHIC FEATURES
GROSS SPECIMENS
MICROSCOPIC FEATURES
MICROSCOPIC VARIANTS
HISTOGENESIS
PROGNOSIS AND TREATMENT
SECONDARY SCLEROSING SARCOMA
SUMMARY

The most highly differentiated periosteal sarcoma is the osteoblastic or sclerosing type This osteoblastic or sclerosing form



FIG. 118. (No. 57632) Roentgenogram showing anteroposterior and lateral views of a sclerosing osteogenic sarcoma in the upper tibia, in a patient of 20 years. The lesion has infiltrated the cancellous bone in the metaphysis and has provoked a periosteal reaction in the lateral and posterior aspects of the tibia.

is the most emphatic bone-forming tumor in the osteogenic sarcoma group since it implicates the end point of ossification, whether the osteogenesis be by the intracartilaginous or membranous route This is indicated microscopically by the proliferation of osteoblasts and new bone †

About one case in five of this sclerosing form of sarcoma may show however under the microscope small islands of cartilage being converted directly into an osteoid state. The presence of this cartilage is explained by the fact that the periosteal tissue from which the neoplasm arises is only a further stage in the development of the primitive perichondrium. On the other hand, the fibrous elements of the preosseous tissue may predominate and in isolated cases these more primitive elements may outweigh the tendency to ossification. This is most often seen in sarcoma of the jaws.

It is this particular tumor characterized in the roentgenograms by dense, shaggy new bone in the periosteal zone in patients between the ages of 10 and 25 years, with which clinicians and roentgenologists are most familiar and which is most commonly diagnosed correctly as sarcoma of the bone

CLINICAL FEATURES

Although the sclerosing form of osteogenic sarcoma with its "sun-ray" appearance in the roentgenogram is the most universally recognized type it is not the most frequent and ranks second, with 187 cases *among a total of 750 osteogenic sarcomas*

Geschickter C. F., and Copeland, M. M. Tumors of bone International Surgical Digest 10: 131 1930

† Knaggs, R. L., and Gruner [illegible] C. A contribution to the study of ossification in sarcomata of bone. Brit. J. Surg. 2: 209, 1914-1915.

Table 17 Osteogenic Sclerosing Sarcoma

Pathologic No.	Race	Sex	Age	Location	Duration, mos.	Symptoms	Treatment	Results of Treatment
62296	W	M	12	Tibia, lower	3	Trauma tumor	Amputation	Well 6 yr
62540	W	F	[illegible]	Tibia, lower	3	Pain tumor		
62002	W	M	23	Humerus, upper	8	Dysfunction 8 mos. pathologic fracture 2 mos.	Amputation	Dead 21 mos.
61908	W	M		Tibia and fibula	3	Trauma tumor	Amputation	Dead 15 mos.
61844		F		Humerus, upper			Amputation	Well 7 yr
61718	W	M	27	Near fibula		Trauma tumor		
61684	W	M	55	Frontal	4	Trauma tumor		Lost
61564	W	M	12	Tibia, upper	1	Pain limp	Amputation	Dead 1 yr
61520	N	M	13	Tibia, upper			Amputation	Well 10 yr
61416		F	16	Tibia, upper	2	Pain	Amputation	Dead 6 mos
61414	W	F	23	Femur lower	10	Trauma 10 mos	Amputation	Dead 2 yr
61146	W	F		Femur lower			Amputation	
60950	W	M	15	Humerus, upper	1	Pain tumor	Amputation	Dead 1 yr
60702	W	M	17	Tibia, upper	2	Pain	Osteotomy and biopsy (amputation refused)	Dead 6 mos.
60332	W	M	17	Femur lower	2	Tumor pain	Irradiation and amputation	Dead 3 mos
60220	W	M	50	Os calcis	0	Recurrent tumor	Original removed previously	Lost
60090	W	F	10	Femur lower	2	Pain tumor		Lost
59956	N	M	76		3	Pain trauma	Aspiration	Dead 1 mo.
59900		F	37	Humerus, upper	3½	Pain	Irradiation	Dead 6 yr
59624	W	F	12½	Femur lower	7	Pain	Amputation	Metastasis to lung. Dead 9 mos.
59388	N	M	14	Femur upper	2	Pain tumor limp		
59268	W	M	49	Humerus	4		Surgery and irradiation	Well 1 yr
59160	W	M		Ilium	[illegible]	Tumor		
58906	W	F	18	Knee	5		Amputation	Dead, embolism 6 hours postoperatively
58574	W	M	19	Knee			Biopsy and irradiation	
58282				Humerus, lower				
57782	W	F	23	Fibula, upper			Amputation	Dead 1 yr
57772	W	F	26	Femur	24	Tumor		Dead 16 mos
57632	N	F	28	Tibia upper	1	Pain	Amputation	Dead 3 yr
57514	W	F	38	Knee	24		Amputation	
57398	W	F	20	Tibia upper	2¼	Trauma pain	Amputation	Well 11 yr
56914	W	M	18	Tibia upper	3	Tumor		Well 12 yr

TABLE 17 OSTEOGENIC SCLEROSING SARCOMA (*Continued*)

Pathologic No	Race	Sex	Age	Location	Duration, mos.	Symptoms	Treatment	Results of Treatment
56326	W	M	42	Femur lower	4	Tumor pain		Dead 1½ yr
56720	W	M	17	Tibia, upper	10	Tumor		
56640	W	F	45	Femur lower	24	Pain		
56414	W		16	Femur			Amputation	Dead 6 mos.
56322	W	M	11	Tibia upper	7	Trauma limp	Amputation	Recurrence 2 yr in humerus
56276	W	M	15	Humerus, lower	18	Tumor	Amputation	
56240	W	M	21	Femur lower	8	Trauma pain limp	Biopsy	Lost
56180	W	F	15	Tibia	3		Amputation	Died 5 mos.
56098	W	M	61	Ilium ribs, sternum skull		Pain		Dead 6 mos.
55787	W	M	59	Ilium			Biopsy	Dead 2 mos
55728	W	F	30	Tibia, fibula	60	Tumor	Amputation	Dead 11 yr metastasis
55602	W	M	32	Humerus	12		Amputation	Well 5 yr
55296	W	F	12	Fibula, upper	1	Pain	Biopsy and irradiation	Dead
55164	W	F	33	Humerus	12		Amputation and irradiation	Dead 2 yr
55142	W	F		Femur lower				
54976	W	M	66	Knee	12		Irradiation	Dead
54900	W	F	9	Leg	3		Exploratory	Died 2 yr
54810	W	M	20	Femur lower				Dead few mos
54728	W	M	23	Femur lower	4	Trauma pain		
54698	W	M	19	Humerus	14		Irradiation	Dead 1 yr
54630	W	M	19	Tibia	14		Irradiation	
54582	W	F	18	Leg			Irradiation and biopsy	Well 8 mos.
54506	W	F	26	Knee	2		Amputation	Dead 20 mos Multiple metastasis
54404	W	F		Femur			Amputation	Dead 1 mo
53842	W	M	14	Scapula	10		Amputation and irradiation	Well 5 yr
53733	W	M		Thigh and hip	6		Irradiation	Dead 3 mos.
53428	W	F	19	Humerus	6		Preoperative irradiation	Dead 6 mos.
53268	W	F	11	Femur lower	2		Curettage and biopsy	Dead 6 wks
53136	W	M	50	Sacrum		Pain		Well 5 yr
52984	W	M		Femur			Amputation, preoperative irradiation	Well 5 yr
52946	W	F	10	Humerus			Amputation	Well 6 yr
52940	W	F	10	Humerus	6	Pain tumor	Amputation	Well 16 yr
52910	W	M	14	Femur	3		Biopsy and irradiation	Dead

TABLE 17 OSTEOGENIC SCLEROSING SARCOMA (*Continued*)

Pathologic No	Race	Sex	Age	Location	Duration, mos.	Symptoms	Treatment	Results of Treatment
51992	W	F		Femur			Amputation	Dead 1 wk, thrombosis
51620	W	F	16	Knee	6		Amputation	Dead
51100	W	F	12	Leg	1			Dead
51034	W	F	13	Tibia	4		Amputation	Well 3 yr
51008	C	M	51	Knee joint	4		Biopsy	Dead 1 mo.
50040	W	F	23	Ilium and sacrum	20	Pain	Irradiation	Dead 2 yr
50000	W	M	23	Fibula	3		Irradiation	Dead
49518	W			Arm			Excision	
49380	W	F	10	Femur	2	Pain tumor	Biopsy and irradiation	Dead 1 yr
49282	W	M	15	Femur	1½			Dead
49160	W	M	20	Tibia	4		Amputation	Dead 8 mos
49044	W	M	8	Fibula	1		Surgery	Dead
49038	W			Humerus	36		Amputation	Well 7 yr
48900	W	M	26	Knee	3		Amputation	
48424	W			Femur			Amputation and irradiation	Dead 3 mos.
48340	W	F	14	Knee	3		Biopsy	
48278	C	M	17	Femur tibia, jaw	8			Autopsy
48148	W	M	40	Tibia	84		Biopsy	
48108	W	F	10	Tibia	5	Pain tumor	Amputation	Dead 1 yr
47948	W	M	65	Tibia	24		Preoperative irradiation	Dead 1 yr
47792	W	M	18	Shoulder	9			Dead 1 yr
47388	W	F	31	Tibia			Excision	Dead 1 yr
47312	W	M	19	Temporal bone	60		Excision	Dead 1 mo
47182	W	F	child	Humerus			Irradiation and resection	Well 16 yr
46922	W	F	9	Humerus	9		Resection and preoperative irradiation	Well 7 yr
46794	W	M	14	Ilium			Biopsy	Dead 4 mos.
46716	W	M	17	Tibia	3½		Amputation and preoperative irradiation	Well 7 yr
46538	W	M	17	Femur	2½		Amputation	Dead 1 yr
46362	W	M	16	Fibula			Amputation and postoperative irradiation	Dead 9 mos.
46196	W	M	13	Femur	3	Pain	Amputation	Dead 1 yr
46028	W	M	16	Femur			Refused surgery	Dead 2 mos.
45934	W	F	22	Skull	36		Excision	Dead 2 yr
45782	W	M	39	Skull	36		Surgery and postoperative irradiation	Lost
45006	W	F	58	Femur	2		Preoperative irradiation and amputation	Lost

TABLE 17 OSTEOGENIC SCLEROSING SARCOMA (Continued)

Pathologic No	Race	Sex	Age	Location	Duration mos.	Symptoms	Treatment	Results of Treatment
44900	W	F	21	Tibia	8		Amputation	Well 7 yr
44606	W	F	37	Femur	84	Tumor	Excision	Dead 3 yr
44422	W	M	20	Femur	24	Pain	Irradiation	Dead 3½ yr
44370	W	M	18	Knee	15		Amputation and irradiation	
44018	W	M	66	Femur	2	Trauma		Autopsy
44006	W	F	10	Humerus	1	Pain	Irradiation	Dead 1 yr
43798	C	F	40	Frontal bone				Autopsy
43756	W	M	25	Femur	2	Pain tumor	Amputation	Dead 2 yr
43642	W	F	45	Tibia	6			
43612	W	M	10	Hand	4		Surgery and irradiation	Well 10 yr

included in this study Among the clinical features of this group the narrow age limits, the characteristic location and the brief duration of the symptomatology are outstanding The majority of patients with sclerosing sarcoma of the bone are between the ages of 15 and 25 years. In the series under analysis, 41 cases occurred in this decade, 36 in the preceding decade (from 5 to 15 years) and 19 in the succeeding decade (from 25 to 35 years) There were 26 cases in persons not in these three decades these were in elderly adults (Tables 17 and 18) Most of the lesions were situated in either the lower end of the femur or the upper end of the tibia, nearly 80 per cent

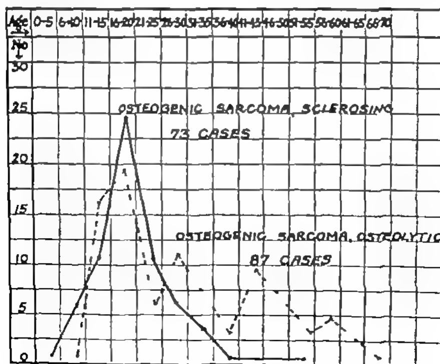


CHART 7 Showing the age distribution of sclerosing sarcoma (solid line) contrasted with the osteolytic form (dotted line)

TABLE 18. OSTEOGENIC SCLEROSING SARCOMA

P N	Race	Sex	Age	Location	Duration, mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Results of Treatment
42832	W	F	33	Femur lower	16	Pain, tumor limp	Sclerosing, periosteal	Amputation, May 1930	Ossification, osteoblasts, spindle cells, cartilage	Dead 1 yr later—met.
42810	W	M	12	Femur	2	Pain, tumor		Irradiation		Dead 1 yr
42180	W	F	17	Femur lower	6	Pain, tumor limp	Sclerosing, periosteal	Amputation, Nov 2, 1929	Ossification, osteoblasts	Dead 1 yr later—met.
41410	W	F	16	Fibula	2	Pain, tumor		Amputation		Dead 1 yr
40878	W	M	18	Tibia, upper right	3½	Tumor pain	Sclerosing, periosteal	Amputation, advised Sept. 12, 1929		
40706				Tibia, upper			Sclerosing, periosteal	Amputation		
40315	W	F	19	Femur lower			Sclerosing, periosteal	Excision, Aug. 15, 1929	Ossification, osteoblasts, spindle cells, cartilage	Well 8 yr
40026	W	F	9	Ilium, right	8	Pain, tumor	Sclerosing, periosteal	Preoperative irradiation; colloidal lead, Jan. 18, 1928		Dead 1 yr
39794	W	M	15	Femur lower right	½	Tumor	Increased density parallel periosteal reaction, spicules	Amputation, December 1927	Ossification, osteoblasts, spindle cells	Dead 1 yr later
39462	W	F	14	Tibia, upper	1½	Pain, tumor		Cauterization, June 20, 1927; amputation, July 16, 1927	Ossification, osteoblasts, spindle cells	Dead 9 mos. after amputation
39252	W	F	16	Humerus, upper	6	Trauma, pain, tumor	Sclerosing, periosteal	Amputation, July 2, 1927		Dead after operation
39114	W	M	21	Femur lower left	3½	Tumor pain	Sclerosing, periosteal	Amputation, April, 1927	Ossification, osteoblasts, spindle cells	Well 14 yr later
38506	W	M		Femur shaft	2		Sclerosing, periosteal	Amputation	Ossification, osteoblasts, spindle cells	Dead 3 yr
38242	W	M	26	Femur lower left	30	Trauma, pain, tumor	Sclerosing, periosteal	Exploration, amputation, Sept. 13, 1926	Ossification, osteoblasts, spindle cells	Dead 18 mos. later
37936	W	M	7	Radius, lower	1	Tumor	Sclerosing, periosteal	Resection May 31 1926 (complete, including end of radius)	Ossification, osteoblasts, spindle cells, cartilage	Dead 6 mos. later
37882	C	M	16	Tibia, upper shaft		Trauma	Sclerosing, periosteal	Amputation, October 1926		Dead 4½ mos. later
37480	W	M	24	10th rib, right	6	Trauma, tumor pathologic fracture	Sclerosing, periosteal	Preoperative irradiation and resection advised, Dec. 20, 1925		Dead 1 yr later
37178	W	F	13	Femur shaft, right	10	Trauma, pain, tumor	Sclerosing, periosteal	Exploration and amputation, Nov 20, 1925	Ossification, osteoblasts	Dead 5 mos. later
37015	W	M	15	Tibia, upper	4	Trauma, pain, tumor	Sclerosing, periosteal	Irradiation advised, Sept. 1 1925		Dead 8 mos. later
36848	W	F	10	Humerus, lower shaft, right	2	Pain, tumor	Sclerosing, periosteal	Exploration and resection, July 10, 1925	Ossification, osteoblasts	Well 18 yr
36113	W	F	13	Humerus, upper			Sclerosing, periosteal	Amputation, Nov 6, 1924	Ossification, osteoblasts, spindle cells	Dead 21 mos. later
35786	W	M	16	Femur upper right	4	Trauma, tumor pain		Amputation, Nov 2, 1924	Ossification, osteoblasts, spindle cells	Dead 3 mos. later
35604	W	M	29	Femur shaft, right	3	Pain, tumor	Sclerosing, periosteal	Irradiation, July 30, 1924		Dead 13 mos. later
35672	W	M	25	Femur lower right			Sclerosing, periosteal	Amputation, Sept. 22, 1924	Ossification, osteoblasts, spindle cells	Local recurrence; dead 7 mos. later
34840	[illegible]	M	16	Femur lower shaft	1½	Trauma, pain		Cauterization, Sept. 6, 1923; amputation, Sept. 21, 1923	Ossification, osteoblasts, spindle cells	Dead 17 mos. later
34834	W	M	15	Femur lower shaft	1½	Pain, tumor	Sclerosing, periosteal	Amputation		Dead after operation
34830	W	M	18	Femur lower	2	Trauma	Sclerosing, periosteal	Curettement, Sept. 3, 1923 amputation, Sept 21 1923	Ossification, osteoblasts, spindle cells	Dead 17 mos. later

34295	W	M	34	Vertebra, 2d and 3d lumbar	18	Tumor pain	Sclerosing, periosteal	Irradiation, 1930	Ossification, osteoblasts, spindle cells	Dead 16 mos. after appearance of symptoms
34104	W	M	22	Femur lower	14	Trauma, pain, tenderness		Amputation, Oct. 26, 1923	Ossification, osteoblasts, spindle cells	Dead 3 mos. later
33423	W	M	10	Scapula, right	4 da	Trauma				Dead 18 mos. after onset
33007	W	M	19	Fibula, upper				Excision, radium, amputation	Ossification, osteoblasts, spindle cells	Dead 5 mos. after excision
32749	W	F	14	Femur lower right	8	Pain, tumor	Sclerosing, periosteal	Irradiation, April 17 1923		Dead 15 mos. later
32132	W	M	18	Femur lower	9	Pain, tumor		Amputation, Jan. 25, 1923	Ossification, osteoblasts	Well 18 yr later
31835	W	M	13	Fibula, upper left			Sclerosing, periosteal	Amputation, Jan. 5, 1923	Ossification, osteoblasts, spindle cells	Well 17 yr
31637	W	F		Femur lower				Excision, Dec. 11, 1922; amputation, Dec. 18, 1922	Ossification, osteoblasts, spindle cells	Dead 11 mos. after amputation
31609	W	F	8	Humerus, upper left	9	Trauma, pain, swelling, pathologic fracture	Sclerosing, periosteal			Dead
30650	N	M	6	Femur lower		Trauma, tumor	Sclerosing, periosteal, some destruction	Exploration, excision		Dead after second operation
30616	W	M	20	Femur upper right	24	Pain, tumor	Sclerosing, periosteal	Exploration, June 17 1922; amputation, Dec. 29, 1922	Ossification, osteoblasts	Dead 1 yr after amputation
30348	W	F	35	Rib, fourth	12	Pain		Irradiation, amputation, Dec. 1, 1921	Ossification, osteoblasts, spindle cells	Well 8 yr later
30169	W	M	12	Femur lower	½	Trauma	Sclerosing periosteal			Dead in less than 1 yr after appearance of symptoms
29863	W	M	23	Femur shaft	48	Swelling				Lost
29000	W	F	25	Femur lower	11	Trauma, pain tumor		Amputation, Nov 4, 1921	Ossification, osteoblasts, spindle cells, cartilage	Dead 6 yr later
28916	W	F	19	Tibia, upper	11	Trauma, pain, tumor	Sclerosing, periosteal, some osseous destruction	Exploration, July 19, 1921; amputation, July 20, 1921	Ossification, osteoblasts, spindle cells	Well 6½ yr later
28353	W	M	67	Ulna, olecranon	16	Trauma, fracture, pain, tumor		Amputation, Dec. 10, 1919	Ossification, osteoblasts, spindle cells	Dead 2 yr 4 mos. later
28221	W	F	34	Femur lower	72	Trauma (6 yrs.), pain, tumor (1 y[illegible])		Amputation, M[illegible]y 1918	Ossification, osteoblasts, spindle cells	Dead nearly 7 yr later
28278	W	F	37	Radius, upper left	48	Fracture 4 yrs.; tumor 1½ yrs.	Sclerosing, periosteal, osseous destruction	Amputation, Jan. 2, 1913	Ossification, osteoblasts, spindle cells	Well almost 12 yr., lost
27743	W	F	20	Femur lower	12	Pain, tumor	Sclerosing, periosteal	Amputation, April 8, 1921	Ossification, osteoblasts, spindle cells	Dead 3 yr., 9 mos. later
27479	W	F	6	Femur lower left		Trauma, pain, tumor pathologic fracture	Sclerosing, periosteal some destruction	Amputation, Jan. 21, 1921; radium and irradiation amputation, May 30, 1921	Ossification, osteoblasts, spindle cells	Well over 9 yr
27223	W	F	16	Skull, parietal left	2	Tumor		Preoperative [illegible]-ray; partial excision, Dec. 30, 1920; postoperative irradiation, radium	Ossification, osteoblasts and early spindle cells	Dead 6½ mos. after operation
27202	W	M	15	Clavicle midpart	3	Trauma, pain tumor	Sclerosing, periosteal, slight osseous destruction	Excision, Sept 1920; preoperative x-ray	Ossification, osteoblasts, spindle cells	Well nearly 10 yr later
26917	W	F	15	Tibia, upper	5	Pain, swelling	Sclerosing, periosteal	Curettement, August, 1920; radium, September 1920		Dead 2 yr after operation



Fig 121 (No 36848) An early case of sclerosing sarcoma occurring in a child of 10 The roentgenograms show new bone localized largely in the subperiosteal region of the metaphysis. In the gross specimen the cortex or the marrow cavity has not been invaded by the tumor The lesion had been present 2 months before treatment, and the patient is living over 10 years after resection of the lower end of the humerus.



FIG. 122. (No. 39114) An early case of sclerosing sarcoma in which subperiosteal formation of new bone in the metaphyseal region predominates. The roentgenogram differs from chondrosarcoma in that slight sclerosis of the marrow cavity is present. The gross specimen shows clearly the fresh white osteoid substance and the slightly increased density in the cancellous bone beneath the cortex. This patient had symptoms of three and one-half months duration, and is living approximately 14 years after amputation.



FIG. 123. (No 45470) Sclerosing osteogenic sarcoma in the lower end of the humerus. This patient was cured by amputation.

months. Trauma, pain, tumor and dysfunction are the usual sequence of events, trauma occurring at the onset of approximately one-half the cases adequately recorded. Pathologic fracture is rare and was listed only five times in the present series. Examination of the affected extremity usually shows a visible and palpable swelling of bony hardness near the end of the bone. Cutaneous changes are not marked over tumors of moderate size, and the slight limitation of motion in the adjacent joint is of no clinical significance. Occasionally crepitus may be elicited by pressure on the bony spicules of the growth, but such manipulations are not to be encouraged when roentgen studies are available.

In one-fifth of the cases leukocytosis or fever or both were recorded, which is about the usual incidence of these systemic reac-



FIG. 124 (No. 30616) A late case of sclerosing sarcoma occurring in a patient, aged 20 who had symptoms of 2 years duration and who died 20 months after an amputation at the hip joint The roentgenogram shows marked sclerosis of the marrow cavity and the gross specimen secondary destruction of the bone with pathologic fracture.

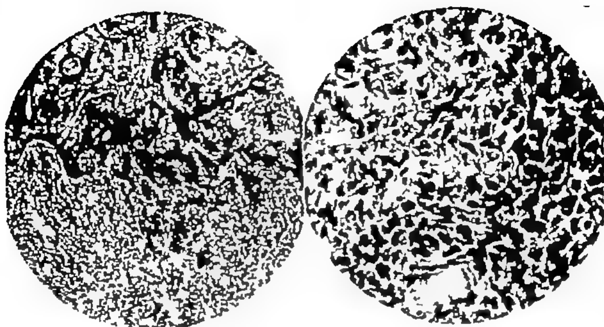


FIG. 125. (No. 30616) Low- and high-power photomicrographs showing the large osteoblasts applied to the osteoid intercellular substance, typical of sclerosing sarcoma. Same case as shown in Figure 124.



FIG. 126. (No. 37938) A gross specimen of sclerosing sarcoma in a boy aged 7. The pronounced formation of new bone which infiltrates into the marrow cavity and soft parts is effectively walled off by the cartilage of the unossified epiphy

tions in rapidly growing malignant neoplasms of the bone whether the patients are seen in the earlier or the later stages of the disease No particular diagnostic importance should be attached to such findings



FIG. 127 (No. 24656) Gross specimen of a cured case of sclerosing sarcoma in a white girl, aged 20 This specimen shows the radiating fibers of the tumor mass proceeding outward from the cortex beneath the periosteum in the metaphyseal region of the bone.

unless the temperature exceeds 101° F and the leukocytes 18,000 above these limits, infection is to be suspected.

ROENTGENOGRAPHIC FEATURES

The roentgenogram furnishes the most helpful diagnostic data available to the practitioner in this group of cases. The roentgenogram in this form of osteogenic sarcoma shows on the shaft side of the epiphyseal line (generally the lower end of the femur or the upper end of the tibia) dense formation of new bone which is obliterating the normal osseous markings. In the marrow cavity this sclerosis is found in a characteristic triangle behind the epiphyseal line and in a subcortical location. It represents the region of junction of two zones of normal ossification that proceeding inwardly from the endosteum and periosteum of the cortex, and that proceeding toward the marrow cavity from the region of the epiphyseal cartilagineus plate. It is accompanied by some secondary destruction which produces a slight mottling effect. In the cortical zone the normal transition between marrow and cortex is obscured by the osseous formation which extends into both medullary and periosteal zones. The periosteum above and below the tumor is raised, and where it resumes its contact with the bone, a triangle of ossification appears, known as periosteal lipping. Although this so-called lipping has been much stressed as a diagnostic feature of sarcoma, it is not rare in forms of periostitis unrelated to neoplastic disease.

The most striking effects are in the region of maximal periosteal separation, where radiating spicules of new bone proceed outward at right angles. These are crowded together to give the characteristic shaggy sun ray appearance (Fig. 120) and in earlier cases, fine lines of new bone at right angles to the cortex appear as "groomed whiskers."

In studying a large series of roentgenograms of cases in which the diagnosis was verified by pathologic examination, the roentgenograms may be grouped according to the duration of symptoms, and the early and late phases of the growth may be compared. In the early cases of from two to four months duration (Figs. 121 and 122) the tumor may be largely confined to a subperiosteal location, in which delicate radiating lines of new bone are visible beneath an area of raised periosteum, the cortex and marrow cavity being practically undis

Fig. 128. (No. 35672) Sclerosing osteogenic sarcoma of the lower right femur The patient was a 25-year-old white male who died with local recurrence 7 months following amputation (*Left*) Roentgenogram shows the lateral view of the lesion (*Right*) Photomicrograph showing osteoid trabeculae surrounded by a profusion of malignant osteoblasts.

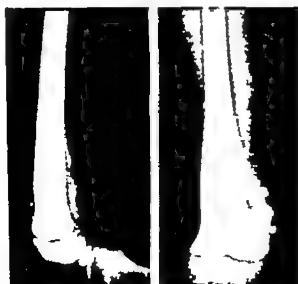


Fig. 129 (No 25195) Roentgenograms showing a sclerosing osteogenic sarcoma of six months' duration in a girl aged 14. The tumor has escaped into the soft parts and there is extensive periosteal lipping.

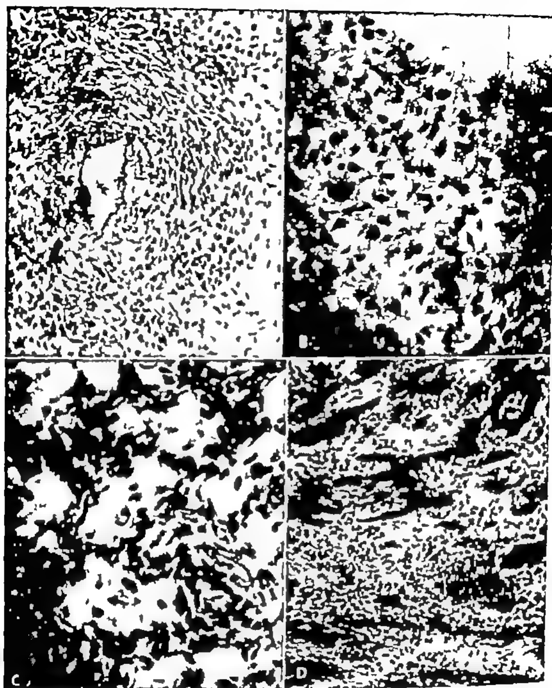


FIG. 130 The histogenetic cycle of sclerosing osteogenic sarcoma (A) shows the preosseous edema among malignant spindle cells and early osteoblasts, surrounding a small blood vessel (B) shows definite osteoid material surrounding the cells which are predominantly osteoblasts; (C) shows the osteoid substance in early and indefinite spicule arrangement surrounded by malignant osteoblasts and spindle cells (D) shows the formation of definite but irregular osteoid spicules, surrounded by a profusion of malignant osteoblasts.



FIG. 131 Roentgenograms of early and late cases of sclerosing osteogenic sarcoma. (A) (No. 60532) Osteogenic sarcoma in a boy of 19 years. The lesion is of 6 months duration and located on the lateral anterior aspect of the lower femur just above the epiphyseal line. It is invading the cancellous spaces producing increased bone density The characteristic right-angle new bone formation and periosteal lipping are seen. (B) (No. 40318) Roentgenogram of a more advanced osteogenic sarcoma in a woman of 22 years. The lesion is located in the lower femur The symptoms had been present for one year The tumor has spread to both sides of the bone through the cancellous spaces and also subperiosteally There is beginning destruction in the marrow cavity This patient died of pulmonary metastases 8 months after amputation.



Fig 132. Gross specimen of a sclerosing sarcoma of the tibia. The tumor occurred in a child, aged 10 The periosteal growth of the lesion exceeds that invading the medullary cavity Note the hemorrhagic spaces in the tumor

turbed. In other cases, the tumor grows neath the cortex and behind the epiphy cartilaginous plate, forming a wedge o creased bone density In the advanced of from 6 to 12 months duration (Figs. and 124) on the other hand, the perios new bone is not only more dense but cortex and marrow cavity beneath are vaded and sclerosed and the growth exte lengthwise along the shaft. Areas of seco ary destruction of the bone and pathol fracture may eventually occur It is c from an analysis of the roentgenograms t *the site of the origin of the tumor is in metaphyseal region in the subperiosteal subcortical zone of the long bones, wh osteogenesis is proceeding most rapidly the age period when these tumors occu*

GROSS SPECIMENS

The gross specimens provide one of most valuable means of studying the or and growth of this type of sarcoma of bone. In all of the specimens availal thirty in all, the tumor proper was situa in the metaphysis, and the epiphysis never primarily involved. In young p tients with an unossified epiphyseal li



Fig 133. (No 42852) The gross specimen of a chondral variant of sclerosing osteogenic sarcoma. The bulk of the tumor mass is lying beneath the periosteum, the marrow cavity has not been invaded.



FIG. 134. (No. 42852) Low power photomicrograph showing the lobular tumor mass ossifying beyond the cortex in the subperiosteal zone. (Same tumor shown in Fig 133.)

the epiphyseal cartilage walls off the tumor in that direction, and even in the advanced stages the epiphysis remains free while the growth extends outwardly into the soft parts and upward along the shaft of the bone (Fig. 126) In older patients, after the epiphysis has united, secondary involvement of the end of the bone occurs when the tumor has progressed without early operative intervention.

In cases in which the bulk of the sarcomatous growth is found between the periosteum and the cortex on the shaft side of the epiphyseal line a focus of tumor tissue also exists in the cancellous bone behind the epiphyseal line The tumor tissue is firm in consistency varying in density from that of solid fibrous tissue to the hardness of compact bone. Its structure shows a definite grain or fiber which runs outward from the shaft, more or less at right angles to its long axis (Fig. 127) The color is white light gray or whitish pink. Hemorrhage, either old or recent, and cyst formation are usually absent, unless the tumor previously has been explored. The ossifying neoplastic tissue is decidedly gritty to the touch and cuts poorly or not at all, when the knife is applied. At its extreme margin the periosteum bounding the tumor may be perforated, and the muscle invaded. This outer zone shows a more fibrillated structure with individual spicules of bone arranged in a radiating manner As the cortex is approached, the tumor is more solid and assumes the structure of compact bone its cut surface often appearing frozen or like caked snow (Fig. 123)

Invasion of the medullary cavity may be primary or secondary to the subperiosteal growth. The earliest change seen in the medullary cavity is the production of normal bone which reacts vigorously to early invasion This sclerosis which is due to a combination of both the tumor

bone and reactive bone, is generally less in amount than the subperiosteal tumor growth, but in rare instances may keep pace with it. As the tumor progresses, the neoplastic tissue gives rise to more and more compact bone which infiltrates from the zone beneath the periosteum, throughout the entire area of the tumor in the medullary cavity and even into the soft parts. It is this picture of diffuse osseous consolidation seen in advanced cases that caused the older pathologists to apply the name of sclerosing sarcoma to this new growth.

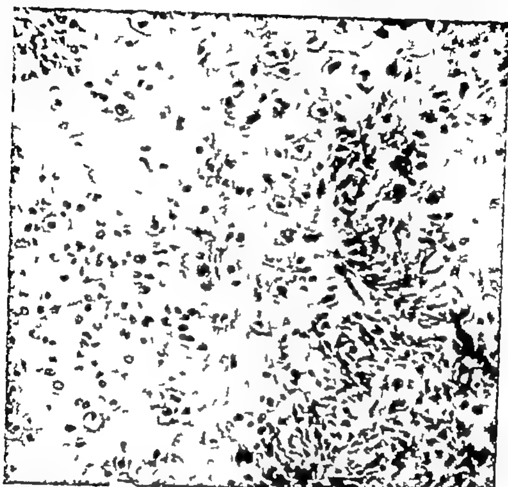


FIG. 135 (No. 42852) High-power photomicrograph showing a cartilaginous area undergoing conversion into osteoid substance. (Same case as in Fig 133)

MICROSCOPIC FEATURES

The microscopic studies confirm the view that the neoplastic process in this sarcoma involves tissue concerned in direct osseous formation. The histology of all these lesions *shows a proliferation* of connective tissue passing through the stages of spindle cells, osteoblasts, osteoid tissue and new bone. *Most of the sections* are dominated by many osteoblasts with large, deep-staining, vesicular nuclei and a cytoplasm pointed in one direction like the tail of a tadpole (Fig 128) Among these cells, a deep-staining osteoid substance is found. This direct ossification differs in these sarcomas from benign reactive bone seen in inflammatory conditions and osteitis fibrosa in two outstanding respects. First, the osteoblasts predominate, and great numbers are packed in among the osteoid tissue in a disorderly fashion. Unlike benign osseous formation of the membranous type, the osteoblasts vary

in size, giving rise to numerous large binucleated forms, and they are not lined in orderly rows about definitely formed bone spicules (compare Figs. 128 and 129) Second, the osteoid tissue is laid down helter skelter and bears no constant relationship to the amount of fibrous tissue or the number of osteoblasts present. In some sections this osteoid substance may infiltrate everywhere, compressing the masses of osteoblasts between it. In other sections the osteoid tissue may be relatively sparse, and the osteoblasts and their precursors, the fibroblasts, may predominate, the osteoid substance being present only in scattered areas (Fig 130)

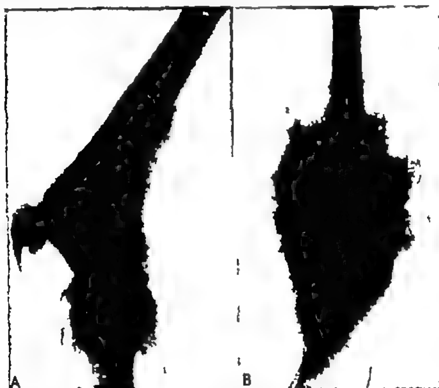


FIG. 136 (No. 37008) A preossifying variant of sclerosing osteogenic sarcoma. (A) shows the roentgenogram before exploration. The tumor mass is seen arising subperiosteally causing periosteal lipping and producing a cloudy extracortical shadow rather than the characteristic picture of sclerosis (B) shows the roentgenogram taken three months after that of (A) There had been four local operations and the tumor is now frankly sclerosing in appearance

MICROSCOPIC VARIANTS

While in the usual sclerosing osteogenic sarcoma, the microscopic features indicate a highly differentiated type of osteogenesis characterized by direct formation of bone with a predominance of osteoid and osseous substance among a proliferation of osteoblasts, some of these tumors despite their periosteal location may show a slightly earlier histogenetic phase

This early phase of the sclerosing form of osteogenic sarcoma may resemble microscopically either primary chondromyxosarcoma or the osteolytic variety of osteogenic sarcoma which arises in cancellous bone. These hybrid or impure microscopic forms involve undeveloped portions of the periosteal connective tissue. When these tumors contain admixtures of cartilage (Fig 135) persisting portions of perichondrium from which the periosteum is derived take part in the new growth, and when ossification is sparse, as in the osteolytic forms of osteo-

bone and reactive bone, is generally less in amount than the subperiosteal tumor growth, but in rare instances may keep pace with it. As the tumor progresses the neoplastic tissue gives rise to more and more compact bone, which infiltrates from the zone beneath the periosteum, throughout the entire area of the tumor in the medullary cavity and even into the soft parts. It is this picture of diffuse osseous consolidation seen in advanced cases that caused the older pathologists to apply the name of sclerosing sarcoma to this new growth.

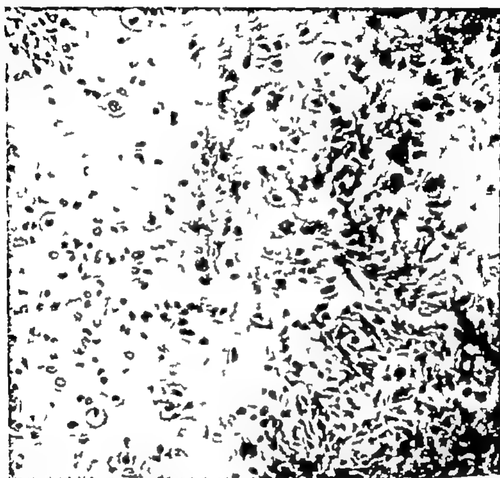


FIG. 135 (No. 42852) High-power photomicrograph showing a cartilaginous area undergoing conversion into osteoid substance. (Same case as in Fig 133.)

MICROSCOPIC FEATURES

The microscopic studies confirm the view that the neoplastic process in this sarcoma involves tissue concerned in direct osseous formation. The histology of all these lesions shows a proliferation of connective tissue passing through the stages of spindle cells, osteoblasts, osteoid tissue and new bone. Most of the sections are dominated by many osteoblasts with large, deep-staining, vesicular nuclei and a cytoplasm pointed in one direction like the tail of a tadpole (Fig 128) Among these cells, a deep-staining osteoid substance is found. This direct ossification differs in these sarcomas from benign reactive bone seen in inflammatory conditions and osteitis fibrosa in two outstanding respects. First, the osteoblasts predominate, and great numbers are packed in among the osteoid tissue in a disorderly fashion. Unlike benign osseous formation of the membranous type, the osteoblasts vary

in size giving rise to numerous large binucleated forms, and they are not lined in orderly rows about definitely formed bone spicules (compare Figs. 128 and 129) Second, the osteoid tissue is laid down helter skelter and bears no constant relationship to the amount of fibrous tissue or the number of osteoblasts present. In some sections this osteoid substance may infiltrate everywhere, compressing the masses of osteoblasts between it. In other sections the osteoid tissue may be relatively sparse, and the osteoblasts and their precursors, the fibroblasts, may predominate, the osteoid substance being present only in scattered areas (Fig 130)



Fig. 136 (No 37008) A preossifying variant of sclerosing osteogenic sarcoma. (A) shows the roentgenogram before exploration. The tumor mass is seen arising subperiosteally causing periosteal lipping and producing a cloudy extracortical shadow rather than the characteristic picture of sclerosis (B) shows the roentgenogram taken three months after that of (A) There had been four local operations and the tumor is now frankly sclerosing in appearance

MICROSCOPIC VARIANTS

While in the usual sclerosing osteogenic sarcoma, the microscopic features indicate a highly differentiated type of osteogenesis characterized by direct formation of bone with a predominance of osteoid and osseous substance among a proliferation of osteoblasts, some of these tumors despite their periosteal location, may show a slightly earlier histogenetic phase

This early phase of the sclerosing form of osteogenic sarcoma may resemble microscopically either primary chondromyxosarcoma or the osteolytic variety of osteogenic sarcoma which arises in cancellous bone. These hybrid or impure microscopic forms involve undeveloped portions of the periosteal connective tissue When these tumors contain admixtures of cartilage (Fig 135) persisting portions of perichondrium from which the periosteum is derived take part in the new growth, and when ossification is sparse, as in the osteolytic forms of osteo-

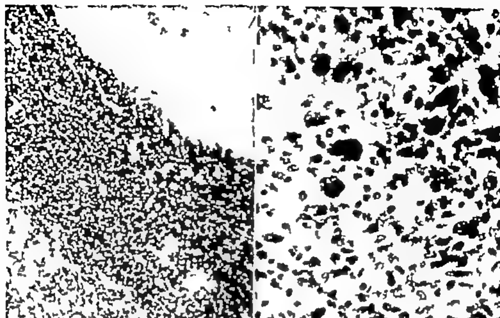


FIG 137 (No. 37008) Low and high-power photomicrograph indicating the histologic structure of the tumor shown in Figure 136. The tissue is very vascular contains many abortive osteoblasts and resembles microscopically an osteolytic form of osteogenic sarcoma.



FIG. 138. (No. 27852) A case of early sclerosing sarcoma classed as a preossifying variant. There is a characteristic roentgenographic appearance. The bulk of the tumor is subperiosteal and of a translucent appearance but secondary bone destruction has occurred in the marrow cavity

genic sarcoma, a juvenile type of preosseous connective tissue is implicated.

Considering the twofold method of bone development in the skeleton, either from precartilaginous connective tissue through cartilage to bone, or from preosseous connective tissue directly to bone it is readily understandable that a neoplasm exhibiting a highly differentiated state of ossification may retain remnants indicating a beginning in either the more primitive precartilaginous or the preosseous state On this basis, the area of cartilage or mixed spindle and round cells found in sclerosing osteogenic sarcoma may be explained. The cartilaginous tissue found in sclerosing osteogenic sarcoma may be clinically disregarded, but when the variation in the histology approaches the microscopic appearance of osteolytic sarcoma, the entire behavior of the tumor in spite of its periosteal location resembles this more primitive variety of neoplasm and hence these cases are similar to those discussed in the next chapter under the heading of the osteolytic form of osteogenic sarcoma.



FIG. 139 (No. 27852) The gross specimen of the case shown in Figure 138 which emphasizes the white fibrous and osteoid substance of the tumor mass and the central hemorrhagic cavity opened up in cancellous bone which is typical for osteolytic sarcoma.

HISTOGENESIS

The evidence accumulated in this study leaves little doubt as to the source of this form of osteogenic sarcoma. The tumor takes its origin in the osteogenic layers of the periosteum or endosteum which are particularly active in the formation of compact bone in the metaphyseal region of young adults and children in the pre- or post-adolescent period. All the roentgenograms and the gross specimens emphasize the predominant metaphyseal location and the subperiosteal origin of these tumors. The fact that this subperiosteal region is not active about the epiphysis after the age of three explains why these ends of the bone are never primarily involved. The midshaft regions are rarely involved in young adults, because the subperiosteal tissue has ceased to function as an active center of growth in this region while metaphyseal growth is at its maximum.

Evidently a normal histogenetic transition from early connective tissue through osteoblasts to osseous formation, occurring at a rapid rate during the period of normal adolescent growth, is necessary for the development of this type of osteoblastic, osteogenic sarcoma. This is borne out by the microscopic studies of this neoplasm, because the histology repeats in all of its essentials the normal formation of bone characterized by connective tissue, osteoblasts and osteoid spicules. It is also con-

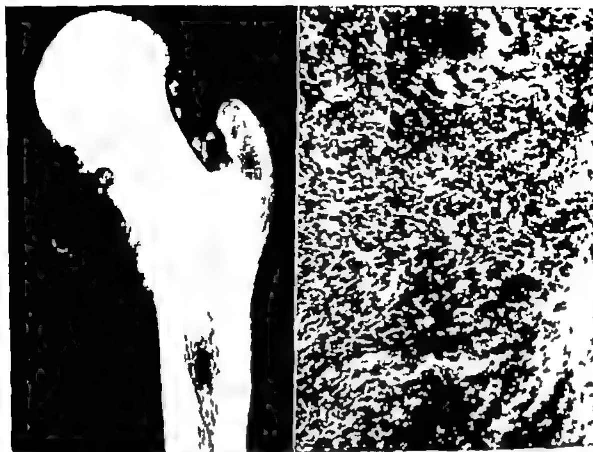


FIG. 140 (No 25761) Sclerosing osteogenic sarcoma of the upper femur The patient was a white male of 18 years. Symptoms had been present 3 months. He died 3½ months following disarticulation. (*Left*) Roentgenogram of the specimen, showing the sclerosis of the neck of the femur and an ossifing mass in the soft parts. (*Right*) Photomicrograph showing the osteoid material in the proliferating malignant connective tissue

firmed clinically by the restricted age period in which these growths occur and their sharply delimited localization in the skeleton

TABLE 19 SCLEROSING OSTEOGENIC SARCOMA

Total Number of Cases	183
Total followed cases	163
Living under five years	10
Total fatal cases	115
Cases well over five years	32
Per Cent five-year cures	21

The mechanism whereby this normal growth becomes malignant is obscure. Trauma is recorded in 50 per cent of these lesions, but no connection can be traced between it and the malignant response. The problem is more difficult because the defensive reaction of the body is performed by a proliferation of the same type of bone that occurs in the malignant process, and this normal bone develops simultaneously with the malignant (Fig. 141)

The growth hormone of the anterior pituitary gland may influence the development of these tumors. Osteogenic sarcoma of the jaw may complicate acromegaly

The feeding of madder (a vegetable dye originally used by John Hunter to study the growth of bone) to patients with this form of sarcoma, has been carried out previous to operation, and the subsequently amputated specimens have been examined. The dye localized in th[illegible] bone

tained the osteoid substance rather the cells concerned in osteogenesis. It therefore possible to confirm the fact the tumor was arising subperiosteally

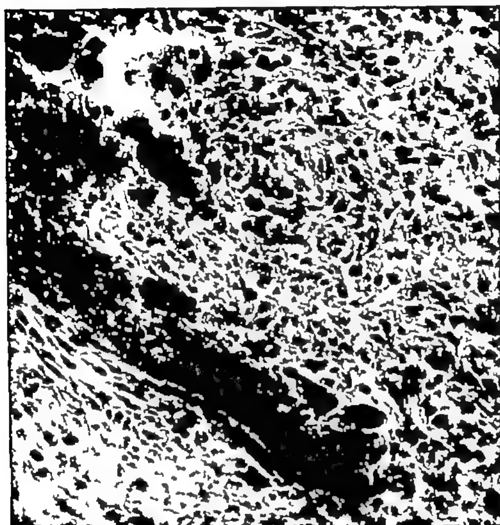


FIG. 141. (No. 27578) Photomicrograph of a section taken from the margin of a sclerosing osteogenic sarcoma showing spicules of normal reactive bone being laid down beside an area of malignant osteoblasts intermingled with early osteoid substance. At the middle of the picture normal bone formation proceeding from the left is meeting malignant bone formation from the right. The result is the destruction of the normal bone spicules and their resorption by giant-cell osteoclasts.

its most actively growing border was the side of the periosteum rather than t to cortical bone, but the differentiation he early malignant cells from embryonic s of normal type concerned in the production of reactive bone was not accomplished (Fig 142)

PROGNOSIS AND TREATMENT

Although the duration of the symptomatology is brief averaging less than 10 months, and the postoperative duration of life in fatal cases averages only 14 months, the percentage of cures effected by radical operation is unusually large in this type of sarcoma. In 147 cases in which complete data were available, including follow up study extending over a period of five years or more, there were 32 cured patients living

five years or longer This is an average five-year survival of 21 per cent. All these cures were affected by radical operation, amputation being performed when possible and radical resection in cases affecting the clavicle or rib In all but two cases, the radical operation was instituted at once. In two of the living patients, however there had been previous aspiration or exploration followed by amputation at an interval of weeks or months.

These data leave no question as to the procedure of choice in this type of sclerosing sarcoma of the bone. Radical amputation or resection should be performed at the earliest possible date, following an exploration under the tourniquet. Frozen sections should be made with an immediate and competent pathologic report, and the operation proceeded with at once. If facilities for frozen sections are not available and consultation is required in the diagnosis, the roentgenograms and not the sections should be sent, as a diagnosis can usually be obtained roentgenologically without the necessity of a preceding exploration, if the proper authorities are consulted.

TABLE 20 DATA ON CASES OF SCLEROSING SARCOMA IN WHICH CURE WAS EFFECTED

Race	Sex	Age	Location	Duration, mos	Symptoms	Treatment	Result
W	M	17	Tibia	3½	Tumor pain	Amputation, middle third of thigh	Well 5 yr
W	F	21	Tibia	8	Pain, swelling	Irradiation, amputation after 4 mos	Well 6 yr
W	M	21	Femur	3½	Tumor pain	Amputation	Well 10 yr
W	F	10	Humerus	2	Tumor pain	Exploration and resection	Well 9 yr
W	M	18	Femur	0	Tumor pain	Amputation	Well 8 yr
W	M	15	Fibula		Tumor pain	Amputation	Well 5 yr 9 mos.
W	F	38	Rib (4th)	12	Pain	Irradiation, amputation	Well 8 yr
W	F	19	Tibia	11	Trauma, pain tumor	Exploration, amputation	Well 8 yr
W	F	27	Radius	48	Fracture 4 yr tumor 1½ yr	Amputation	Well 11½ yr (lost)
W	F	6	Femur		Trauma, pain tumor pathologic	Aspiration, radium and fracture irradiation amputation	Well 9 yr
W	M	15	Clavicle	3	Trauma, pain tumor	Resection, preoperative irradiation	Well nearly 10 yr
W	F	7	Femur	2	Tumor trauma, pain	Exploration, amputation	Well 6 yr (lost)
W	M		Femur		Tumor fracture	Amputation	Well over 17 yr
W	F	24	Femur	18	Trauma, pain, tumor	Amputation	Well over 16 yr
W	F	11	Tibia	1½	Tumor	Amputation	Well over 14 yr (lost)
W	F	25	Femur	11	Trauma, pain	Amputation	Dead 5½ yr phlebitis in other leg
W	F	19	Femur	5	Pain, tumor	Amputation	Dead 5 yr later from eclampsia
C	F	13	Mandible	9 wks.	Tenderness, loose teeth	Resection	Well 25 yr

Deep roentgen therapy does not result in cure in these cases and only restricts the rate of advance of the peripheral margin of the lesion. Two of the patients considered cured had received Coley's toxins in addi- and stilbesterol (5 mg daily) was given by mouth, combined with calcium diphosphate and vitamin D.*

In a patient with a sclerosing sarcoma of the bone, in a limb or resectable bone re-



FIG. 142. (No. 43060) Roentgenogram and gross specimen of a case of sclerosing sarcoma occurring in a white man, aged 49. This patient was fed a madder diet on four consecutive days preceding amputation. The result is depicted in the gross specimen. The growth of the tumor at its periphery is shown by the dark areas, the recent osteoid substance having taken up the red dye and staining this portion only. The dye unfortunately had faded somewhat when the photograph was made and is indicated by the arrows. The other dark spots are hemorrhage. In this case the original tumor is in the metaphysis but has spread up the shaft.

tion to radical operation. Three had also had the benefit of postoperative irradition.

In a small series of sclerosing osteogenic sarcomas, and in those of the osteolytic variety as well, in which the tumor was inoperable, either because of recurrence, metastases or extension, the authors have secured palliation over a period of from one to three years by administering estrogens. Estradiol pellets of 50 mg. were implanted, gardless of age, the chances of cure are about 21 per cent, when primary radical operation is performed. This probability of a cure becomes less the longer the duration of symptoms prior to operation and the greater the interval of time elapsing between an incomplete primary operation

* More recently estrogen has been combined with calcium decyl phthalate given orally and parenterally in 100 mg. doses daily.

and radical treatment. It can also be stated that patients surviving radical operation after eighteen months, who show no signs of recurrence or metastases at that time, will, in all probability remain free from disease.

SECONDARY SCLEROSING SARCOMA

The clinical data just reviewed indicate that the usual sclerosing osteogenic sarcoma, whether microscopically typical or representing one of the variant forms described, arises de novo during the active



FIG. 143 (No 28352) Roentgenogram showing a fracture of the right ulna in a white man, aged 67 in which sclerosing sarcoma is arising in the callus. The fracture occurred one year previous to the symptoms of tumor formation. The patient died of metastases two and one-half years after amputation at the shoulder girdle

This high percentage of five-year cures in osteogenic sarcoma is unusual, and the better prognosis in patients with the sclerosing form depends on the state of differentiation of the malignant cells or osteoblasts which represents the apex of development in the derivation of bone from connective tissue The better prognosis in these sarcomas is in keeping with the general rule that the higher the state of differentiation in the neoplastic tissue, the less malignant is the clinical course

period of growth Practically all the patients are between 15 and 35 years. There are, however a few exceptions (6 among 100 cases) patients who are beyond the period of growth, and the inference is that the malignancy is secondary to primary benign lesion

This is definitely indicated by the data in one of the cases. In this instance, a white man, aged 67 (Fig 143) had fractured his right elbow one year previously The roentgenogram showed a distinct ununited frac-

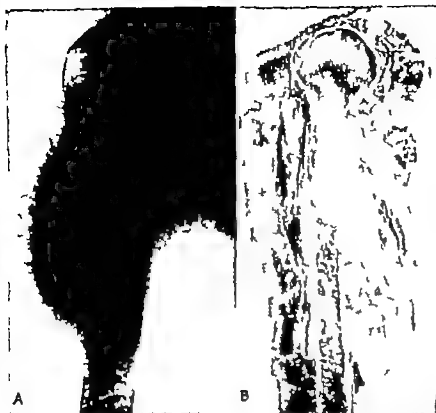


FIG. 144 (No. 36014) A case of myositis ossificans undergoing secondary change into sclerosing osteogenic sarcoma in a white man, aged 28. (A) taken in October 1923 depicts the formation of new bone of a laminated character in the soft parts, typical of myositis ossificans traumatica, but in addition there is periosteal reaction indicating early malignancy (B) shows the specimen amputated in July 1928. The picture shows a fully developed sclerosing sarcoma which has infiltrated the marrow cavity



FIG. 145 (No 36014) Roentgenogram showing consolidation of the upper right side of the chest by tumor metastases occurring in March, 1929 in the same case shown in Figure 144.

ture with diffuse callus formation about the upper end of the ulna. In this callus formation a secondary malignant change occurred, and the patient died of metastases two and a half years after an amputation at the shoulder girdle.

of secondary sarcoma arising in the callus of a fracture.

Two other instances of secondary sclerosing osteogenic sarcoma arising in myositis ossificans are illustrated (Figs. 145 to 147) A case of acromegaly with osteogenic sar

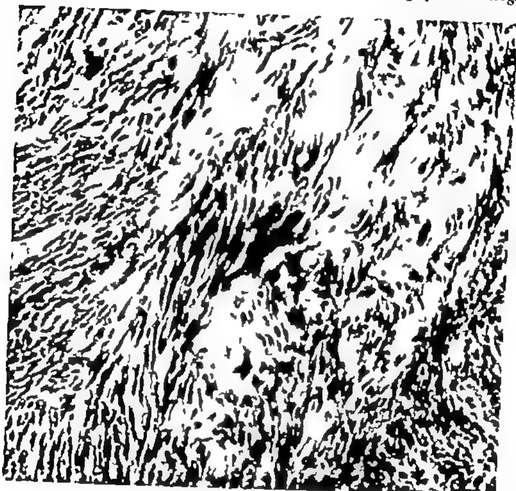


FIG. 146 (No 36014) Photomicrograph showing malignant new bone in the case illustrated in Figures 144 and 145

coma of the jaw is also recorded in the laboratory In still another case, a woman of 45 had an old osseous defect in the femur the site of fibrous dysplasia. Malignant change took place after 25 years.

In another case, a white woman, aged 38, complained of acute pain in the left side of the chest which was more intense on coughing A brace was applied to the chest, roentgen therapy was given, and the lesion became apparently better A year later the symptoms recurred, and a roentgenogram revealed an osteogenic sarcoma arising over the fourth rib in the axillary line. Although the examination was performed elsewhere and no inquiry was made in regard to trauma, the history suggests that this was apparently another instance

These instances of sclerosing, osteogenic sarcoma arising secondarily to benign lesions are in keeping with the evidence studied in regard to the other forms of osteogenic sarcoma. Both chondrosarcoma and the osteolytic varieties may arise as primary or secondary lesions, (either may complicate Paget's osteitis) and to the

sclerosing form must also be ascribed such possibilities.

SUMMARY

This is a highly differentiated form of osteogenic sarcoma composed of osteoblasts and is sclerosing in type according to the recognized as the "sun ray" type of sarcoma of bone. It is most frequent between the ages of 15 and 25 years, predominates in the lower femur and the upper tibia, and runs a fairly acute course, with symptoms initiated by trauma followed by pain, tumor and dysfunction The average dura



FIG. 147 (No. 27702) A case of osteogenic sarcoma developing in myositis ossificans about the upper end of the fibula in a white woman, aged 34. (A) taken in October 1919 shows the ossifying periosteal mass with signs of malignant change. (B) shows the recurrent malignant growth in October 1922, three years after a resection of the upper third of the fibula. This patient was living eight years following an amputation for the recurrence This case was reported by Paul (Arch. Surg. 10: 185)

terminology of Virchow While this form of sarcoma does not ordinarily contain cartilage, it is derived from the primitive perichondrium after this structure has been transformed into periosteum and may rarely show cartilage formation.

This tumor is characterized in the roentgenogram by dense radiating new bone in the periosteal zone in the metaphysis of the long bones of youthful patients, and is tion of symptoms is under 10 months. The tumor is essentially a proliferation of new bone proceeding from the subperiosteal region of the metaphysis, raising the periosteum on the outward side and infiltrating the marrow cavity inwardly Both the roentgen and the gross specimen depict this and have a characteristically sclerosed appearance.

Histologically the tumor is composed

large osteoblasts derived from connective tissue with much intercellular osteoid substance scattered in a disorderly fashion throughout the growth. The neoplasm is an exaggeration of the function of osteogenesis which resides in the primitive connective tissue of the subperiosteum and endosteum. It arises during the age period and at the site where this subperiosteal tissue is active. This tumor is, therefore, characteristically limited to the postadolescent age period and to the metaphyseal region of the long bones. Permanent cures can be achieved in approximately one-fourth of these cases by prompt resection or amputation. Deep roentgen or radium therapy is not advised, for this tumor gives no evidence of being radiosensitive.

In elderly adults an unusual secondary form of sclerosing osteogenic sarcoma may occur. The preceding lesion is either fibrous dysplasia or myositis ossificans. In its pathology it resembles the more common primary form. This is a rare occurrence.

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See also Bibliography, Chapter 6.

9

Osteolytic Forms of Osteogenic Sarcoma—Osteolytic Sarcoma

Osteolytic sarcoma arising in cancellous bone is not frequently described as a separate entity although it has long been recognized as a source of confusion in the diagnosis of tumors of bone. In the older treatises on pathology from the time of Virchow up until about 1910 this form of tumor was either referred to as a malignant cyst or aneurysm of the bone or it was described histologically as an angiosarcoma. The term "malignant bone aneurysm" and telangiectatic sarcoma can easily be understood if one is familiar with the pathology of these lesions, since this form of sarcoma is essentially a central destructive growth in which a mass of necrotic bone within the confines of a cortical shell is replaced by vascular tissue However as far back as 1876, it was recognized that this was in all probability not a vascular lesion in the bone but a true neoplasm. Sir James Paget, in his lectures on surgical pathology in 1876 wrote in regard to aneurysms of bone and the so-called osteo-aneurysms

> I am far from convinced that, in all the cases thus entitled, the blood vessels of the bone were primarily or chiefly diseased. My impression is that in many of them the disease was really medullary cancer or myeloid tumor of the bone with large development of vessels, and that in some it was such a blood cyst as appears to be sometimes formed in the course of a myeloid or cancerous disease

Notwithstanding the early origin and the extent of the literature that has accumulated on this subject, this form of sarcoma is rarely recognized in the roentgenogram. Even with the aid of microscopic examination, competent surgeons and pathologists are repeatedly diagnosing this lesion either as a form of osteitis fibrosa or of giant-cell tumor This mistake accounts for several reports of so-called metastatic giant-cell tumors that have occasionally crept into the literature (Geschickter and Copeland†)

CLINICAL FEATURES

The clinical features of osteolytic sarcoma are marked by a wide age distribution, by variability of the region of the bone involved and by frequency of pathologic fracture The incidence of the disease is maximal between the ages of 10 and 20 and falls away gradually in the later decades, but it may occur at any age. Like other forms of osteogenic sarcoma, the disease is most prevalent in the long bones and most frequently affects the lower end of the femur and the upper end of the tibia (Fig 148) With the exception of pathologic fracture, which occurs in approximately 50 per cent

Paget, James Lectures on Surgical Pathology London, Longmans Green and Company 1876, Lecture XXVII p. 553, footnote

† Geschickter C. F., and Copeland, M. M Recurrent and so-called metastatic giant cell tumor Arch. Surg. 20: 713, 1930.

OSTEOLYTIC OSTEOGENIC SARCOMA

Fig. 148. Skeletal chart showing the distribution of osteolytic osteogenic sarcoma. The black areas show the most frequent sites the checked areas the common sites and the diagonal lines, occasional involvement.

of all cases, the symptomatology of this group of neoplasms is not characteristic. Trauma without etiologic significance is the initial event in less than 25 per cent of the lesions, and the usual sequence of symptoms is pain tumor limp trauma and fracture.



Fig 149 (No 39278) A case of osteolytic sarcoma of the upper end of the humerus occurring in a white man, aged 22, who died two months after a primary amputation. This figure shows the large boggy swelling over the upper end of the humerus characteristic of this type of neoplasm, referred to in the old literature as malignant aneurysm of the bone.

The average duration of symptoms is slightly under one year prior to the initial treatment (Tables 21 and 23)

As in the other forms of sarcoma of the bone, evidence of a systemic reaction in the form of fever and leukocytosis may be observed at any time during the clinical course. The temperature may range between 99° and 102° F., and the leukocytosis from 11,500 to 17 000. The regional lymph nodes may be enlarged, and in one instance metastatic involvement was microscopically proved. Such metastatic involvement of regional nodes by any form of sarcoma is rare.

TABLE 21 OSTEOGENIC, OSTEOLYTIC SARCOMA

Pathologic No	Race	Sex	Age	Duration, mos.	Location	Symptoms	Treatment	Results of Treatment
62668	W	F		6	Tibia	Pain	Amputation	Living 4 yr
62612	W	M	25	54	Vertebrae	Pain		
62558	C	M	20		Ischium			Dead 4 mos.
62476	W	M	34	24	Knee	Pain	Biopsy	Dead 7 mos.
62400	W	F	33		Tibia, upper		Amputation	Living 5 yr
62189	W	M	32		Tibia, upper		Amputation	
62058	W	M	25		Tibia, upper		Amputation	
62672	W	M	7	1	Tibia	Tumor	Biopsy	Dead 4 mos.
62028	W	M	35	5	Femur lower	Tumor pain		
61784	W	M	17		Femur		Amputation	Lost
61104	W	F	42		Fibula, lower			
61134	W	M	16	1½	Femur	Tumor	Biopsy	Dead 8 mos.
61130	W	F	22	4	Ischium	Trauma, pain		Dead 6 mos.
61000	W	M	10		Fibula upper		Biopsy	Lost
60054	W	F	37	9	Femur		Exploration curettage and irradiation	Dead 2 yr
60700	W	F	16		Femur		Amputation	Living 9 yr
60038	W	M	10	3	Femur	Trauma		
60632	W	M	33		Tibia, upper		Amputation	Living 9 yr
60568	W	F	10	6	Phalanx of great toe	Trauma	Amputation	
59399	W	F	7		Tibia, upper	Trauma, fracture		
58810	W	M	65					Dead
58348	W	M	13	½	Femur lower	Tumor pain	Amputation	Dead 1 yr
57864	W	M	9	¾	Tibia, upper		Amputation	Living 11 yr
57288	W	F	15	6	Femur lower	Trauma, pain	Irradiation	
57448	W	M	20	16	Femur lower	Dysfunction pain	Irradiation	Lost
57176	W	M	21		Radius, lower		Resection	Well 12 yr
56450	W	F	12		Femur		Amputation	
56324	W	M	43	10	Tibia, upper	Pain	Amputation	Dead 3 mos. metastases
56298	W	M	21	12	Tibia, upper	Trauma	Amputation, irradiation	Lost
56104	W	M	63	36		Pain, tumor	Amputation	Dead, 5 mos.
56024	W	F	12	3	Femur	Injury fracture	Amputation	Dead, 22 mos., metastases
55056	W	M	58	24	Femur clavicle	Pain	Biopsy	Dead, 2 mos.
55136	W	M		[illegible]	Fibula upper	Tumor pain	Amputation	Dead 8 yr (scarlet fever)
54556	W	F	60		Ilium			
53263	W	F	11	2	Femur lower	Tumor		Dead 5 mos.
52314	W	M	18	1	Radius, lower	Pain	Amputation	Dead [illegible] mos., metastases
52112	W	M	20		Shoulder		Biopsy	
52105	W	F	45		Femur lower		Operation	Dead post operative embolism

TABLE 21 OSTEOGENIC, OSTEOLYTIC SARCOMA (Continued)

Pathologic No	Race	Sex	Age	Duration mos.	Location	Symptoms	Treatment	Results of Treatment
52106	W	M	75	18	Tibia, lower	Pain	Irradiation	Dead, 2 yr metastases
51992	W	F	54	3	Femur lower	Tumor	Amputation	Dead, 1 wk, postoperatively
51708	W	M	22		Humerus		Preoperative irradiation	Dead
51692	W	M	13	0	Scapula	Tumor		Lost
51674	W	F	59	11	Os calcis	Tumor	Amputation	Lost
51620	W	F	16	6	Femur lower	Tumor		Lost
51372	W	F	21		Tibia, upper			Dead, immediately
51202	W	M	61	6				Dead, 2 mos
51006	C	M	51	4		Pain	Amputation	
49486	W	M	57	6	Scapula	Tumor	Excision and irradiation	Dead, 2 yr
49656	W	M	18	24	Leg			Dead
49160	W	M	20	4	Tibia, lower	Trauma tumor	Amputation	Dead, 8 mos metastases
48136	W	F	26	5	Humerus	Trauma, fracture	Amputation, preoperative irradiation	Well, 5 yr
47954	W	F	19	15	Humerus		Amputation, preoperative irradiation	Dead, 2 yr metastases
46840	W	M	26	2	Femur		Amputation	Dead, 1 yr
46384	W	F	16	2	Tibia		Refused treatment	Lost
44098	W	F	62	36	Ilium			Dead
44092	W	M	66	168	Fibula	Trauma	Amputation and irradiation	Dead 4 yr
43268	W	F	72		Femur			Dead
43166	W	M	11		Femur		Amputation	Dead, 1 yr
43060	W	M	49	12	Knee		Amputation	Dead, 1 yr
47868	W	M	52	18	Ilium femur upper tibia upper	Pain	Irradiation	Dead, 10 days
47182	W	F			Humerus		Resection	Lost
46028	W	M	16	6	Femur	Pain	Amputation refused	Dead, 1 yr

The common origin of these growths is in the subcortical region of the metaphysis. The lesion, however rapidly invades cancellous bone and the medullary spaces so that when examination is delayed the disease extends to a more central location, and the epiphysis or the shaft is involved. Once the new growth has reached the epiphysis, destruction of the bone is sufficiently advanced to create the typical vascular cavity suggestive of an aneurysm, and pulsation with symptoms referable to the joint may occur

Examination of the affected limb reveals a swelling, over which the skin is movable but tense, without much reddening (Figs



FIG. 150. (No. 39278) Roentgenogram of the lesion shown in Figure 149 The upper end of the humerus has been replaced by a hemorrhagic mass of neoplastic tissue which has infiltrated into the soft parts.



FIG. 151 (No 39278) Gross specimen showing the hemorrhagic character of the neoplasm and its bone-destructive tendencies. (See also Figs. 149 150 152.)

149 150 151, 152) The superficial veins may or may not be dilated, depending on the size of the growth. On palpation, the peculiarity of these tumors is their boggy feel and the suggestion of semifluctuation. Pulsation, when present, immediately brings to mind the old clinical entity of malignant aneurysm of the bone Limitation of motion may occur in the adjacent joint, but excess fluid in the joint cavity or actual involvement of the joint rarely occurs. In half of these cases an ununited pathologic fracture is present.

ROENTGENOGRAPHIC FEATURES

The roentgenograms of this osteolytic form of sarcoma of bone are extremely difficult to interpret. These lesions are confused with benign cyst of the bone benign giant-cell tumor metastatic carcinoma of bone and Ewing's sarcoma, even by those experienced in roentgenologic diagnosis. Among those less experienced, the mistake of confusing this tumor with osteomyelitis is common.

The most important diagnostic feature in the roentgenograms is the central area of irregular destruction which extends through the unexpanded cortex resulting in a periosteal reaction. The early and late manifestations of the disease present different diagnostic problems from the roentgen standpoint.

In the early cases (Figs 153, 154, 155 157) the destruction is subcortical and metaphyseal and slightly expands the cortical bone thinning it and causing perforation or melting away The age of the patient, the osteolysis, and the central, metaphyseal character of the lesion immediately suggest the possibility of a benign cyst.

TABLE 22 OSTEOGENIC OSTEOLYTIC SARCOMA

P N	Race, Sex and Age	Location	Duration, mos	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Results of Treatment
42844	W F 20	Femur lower	3	Pain, tumor six weeks	Destruction in condyle, translucent periosteal shadow	Amputation, September 1929	Early osteolytic	Metastases to chest 6 mos. later
43614	(Monkey)	Radius, head		Pain, tumor	Osseous destruction	Amputation	Mixed, spindle and round cells with giant cells	Dead
43418	W F 16	Tibia, upper	½	Tumor	Resembling osteomyelitis	Incision and drainage, November 1929; excision, November 1929; curettement, December, 1929; curettement, May 1930		Dead 3 yr later
41364	W F 14	Ilium, right	2	Tenderness, limp	Osteolytic zone	X-ray, April, 1929		Dead
41194	W M 12	Tibia, upper left	12	Trauma, fluctuating tumor	Subcortical, expanded osteolytic	Curettement, December 1928; amputation	Large spindle cells, pleomorphic osteoblasts	Well 9 yr later
40813	W M 33	Humerus, upper		Pathologic fracture		Amputation, March 9, 1927		Lost
40763	W M 40	Femur lower right	24	Pain, trauma, pathologic fracture	Osseous destruction perforation of shell, some formation of bone	Exploration, March 24, 1917; amputation, Jan. 21, 1925	Large spindle cells, pleomorphic osteoblasts	Dead 1 yr after operation
40766	W M 24	Tibia, upper left	12	Trauma, pain, swelling	Involvement of knee joint, destruction, some osseous formation bone shell of tibia gone	Curettement, 1917; curettement, 1919; amputation, 1921	Mixed, round and spindle cells with giant cells	Dead November 1922
40528	W M 13	Tibia, midportion	½	Trauma, swelling, pain	Sclerosing periosteal shadow with central destruction	Curettement, April 4, 1928; amputation, June, 1928	Large spindle cells; pleomorphic osteoblasts; giant cells	Dead
40440	W M	Humerus, upper	4	Pain, tenderness	Mottled slight destruction	Excision of gland, March 1928		Dead 3 mos. later; autopsy general metastases
39970	W M 35	Femur upper	7	Pain since September 1926 limp	Mottled slight destruction	Operation advised against		Dead 2 yr.
39814	W M 38	Humerus, upper right	6	Pain, tumor	Osseous destruction, soft part shadow	Amputation, Sept. 30, 1927	Malignant spindle cells, few osteoblasts	Dead 7 mos. later
39273	W M 22	Humerus, upper left			Osseous destruction with a little formation of bone; large soft part shadow, metastases to chest (?)	Amputation, June 2, 1927	Large spindle cells, pleomorphic osteoblasts	Dead 70 days later
38834	W F [illegible]	Femur, left lower	4½	Pain, trauma	Osseous destruction, right angle formation of bone	Biopsy May 1927	Large spindle cells, pleomorphic osteoblasts, many giant cells	Dead 2½ yr
36028	W M [illegible]	Humerus, upper left	5	Trauma, pain, tumor				Dead 6 hr. after examination
33862	W F 17	Tibia, upper right			Much osseous destruction right angle formation of bone	Resection, June, 1927		Well 14 yr later
38670	W F 16	Humerus, upper left	3	Trauma, pain, tumor fracture	Osseous destruction, right angle formation of bone soft part shadow	Amputation, Feb. 2, 1927	Malignant, spindle cells, osteoblasts; few giant cells	Dead 5 mos. later
36236	N M 75	Fibula, lower left	9	Pain, tumor	Osseous destruction, formation of bone, periosteal reaction	Amputation, July 24, 1926	Malignant, spindle cells, osteoblasts	Lost

29318	W	M	72	Femur lower	6	Pain, swelling	Central cyst, roughened cortex	Amputation, July 1928		Dead 5 mos. later
35182	W	F	44	Femur			Osseous destruction, formation of bone	Amputation, July 14 1926	Many malignant spindle cells, few pleomorphic osteoblasts	Dead 1 yr
27614	W	F	45	Femur shaft, right	3	Pain, fracture	Osseous destruction	Amputation, March 23, 1927; curettement, Jan. 23, 1926	Malignant spindle cells, few osteoblasts	Recurrence after curettement; dead 11 mos. after amputation
27516	W	M	61	Tibia, mid-part, right		Pathologic fracture	Pathologic fracture, callus	Amputation advised		Well 11 yr later
27079	W	M	15	Femur lower left	3	Trauma, tumor	Periosteal reaction with osseous formation and destruction, soft part shadow	Exploration 4 times in two months; amputation, Aug 20, 1925	Malignant spindle cells; pleomorphic osteoblasts	Dead 3 mos. later
26721	W	F	10	Tibia, lower shaft, right	9	Pain, tumor	Osseous destruction and expansion with cystic areas	Exploration, 1924; amputation advised, 1925	Pleomorphic osteoblasts	Dead 1 yr
26156	W	M	39	Femur upper shaft, right	9½	Trauma, pain, pathologic fracture	Osseous formation and destruction with expansion involving the shaft radiating bone	Preoperative radiation; amputation, April 21 1925	Malignant spindle cells and pleomorphic osteoblasts	Dead 3 yr later
25798	W	M	15	Femur lower	11	Trauma, repeated; tumor		Amputation	Malignant spindle cells, pleomorphic osteoblasts, osteoid tissue	Dead 5 mos. later
25217	W	M	20	Fibula, lower	36	Tumor pain	Destruction, periosteal roughening	Exploration, April 21, 1924; amputation, May 10, 1924		Dead 1 yr later
25095	W	M	24	Humerus, upper right	2	Pain, swelling	Mottled-periosteal lipping	X-ray December 1923		Dead 1 yr later
24539	W	F	24	Femur lower right	6	Trauma, pain, swelling	Osteoporosis, formation of bone	Amputation, Dec. 1 1923		Dead 4 mos. later
24522	W	M	20	Tibia, upper right	3	Swelling, pain	Osteoporosis and destruction	Amputation, June 2, 1923	Mixed, spindle and round cells	Dying with metastases Sept. 12, 1924
24420	W	M	18	Tibia, shaft, upper	12	Trauma, pain, tumor		Amputation, Dec. 13, 1923	Malignant, spindle cells	Dead 9 yr
24234	W	M	12	Femur lower	12	Pain, swelling	Central destruction, onion-peel periosteal appearance	Curettement, Nov 23, 1923	Malignant, spindle cells, pleomorphic osteoblasts, much osteoid material	Dead 1 yr 3 mos. later
24070	W	F	15	Humerus, upper	3	Pain, swelling	Destruction, raised periosteum	X-ray; amputation, August, 1923		Dead 4 mos. later
23823	W	M	40	Femur lower shaft	4	Pain, pathologic fracture		Exploration, Sept 11 1922; amputation, Sept. 22, 1922		Dead 1 yr 3 mos. later
23812	W	M	11	Femur lower right	1	Trauma, pain, pathologic fracture		Exploration, Feb. 4, 1922; irradiation, April 21, 1922; amputation, May 1922	Malignant spindle cells, pleomorphic osteoblasts with giant cells	Dead 6 mos. after amputation
23808	W	F		Femur lower			Resembling giant cell tumor	Amputation, December 1921	Mixed, spindle and round cells with giant cells	Recurrence; dead 10 mos. later
22883	W	M	20	Humerus, upper	4	Pain, trauma, fracture		Exploration, Dec. 6, 1922; amputation, April 17 1923	Malignant spindle cells, pleomorphic osteoblasts	Dead 5 yr 3 mos. later
22778	W	M	20	Humerus, lower	1	Trauma, pain, tumor	Destruction, roughened periosteum	Incision, Nov 10, 1922; amputation Dec. 12, 1922		Dead 10 mos. later

TABLE 22. OSTEOGENIC, OSTEOLYTIC SARCOMA (*Continued*)

P N	Race, Sex and Age	Location	Duration, mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Results of Treatment
32093	W M 14	Tibia, upper right	1	Trauma, pain, tumor		Curettement, June, 1920; amputation, July 1920	Malignant spindle cells, pleomorphic osteoblasts with giant cells	Dead 4 mos. later
31880	W M 35	Tibia, lower	7	Pain, tumor	Central destruction	Curettement, 1906; amputation, 1909	Mixed spindle and round cells, with giant cells	Dead 7 yr later
31695	W F 16	Femur mid-part	1½	Pain, swelling	Osseous destruction with roughened periosteum			Dead
31333	W F 16	Femur lower shaft	3	Pain, tumor		Curettement, August, 1922; irradiation; amputation, Jan. 6, 1923	Malignant spindle cells, pleomorphic osteoblasts with osteoid material	Dead 3 yr., 11 mos later
30189	N F 20	Tibia, mid-part	8	Swelling, pain, pathologic fracture	Diffuse destruction, some osseous formation	Excision, Aug. 4, 1921 amputation, Aug. 5, 1921		Dead 2 mos. later
29400	W M 23	Femur lower left	10	Pain, tumor		Exploration, Jan. 6, 1922; amputation, Jan. 10, 1922	Malignant spindle cells, pleomorphic osteoblasts	Dead almost 3 yr later
[illegible]	W M 21	Femur lower right	4	Trauma, pain, swelling	Destruction of bone shell	Excision, Feb. 4, 1921; curettement, March 5, 1921; amputation, April 20, 1921	Large spindle cells, pleomorphic osteoblasts	Dead 4 mos. after amputation
[illegible]	W F 67	Femur lower right	6	Pain, swelling, pathologic fracture	Great destruction	Amputation, July 12, 1921	Large spindle cells, pleomorphic osteoblasts	Dead 1 mo. later
27761	W M 27	Ischium	24	Trauma, swelling	Destruction of ischial ramus	Curettement, March 21	Large spindle cells, pleomorphic osteoblasts	Dead almost 2 yr later
29084	W M 58	Femur, upper left	4	Pain	Osseous destruction and onion-peel formation	Exploration, Oct. 20 1921; amputation, June, 1924		Dead
28015	W F 14	Tibia, upper	2	Pain, tumor		Amputation, October, 1921, after curettement, August, 1921	Malignant spindle cells, pleomorphic osteoblasts, infection	Dead 4 mos. after amputation
28574	W F 49	Femur lower	12	Pain, tumor pathologic fracture	Extensive destruction	Amputation, March 17 1922	Malignant spindle cells, pleomorphic osteoblasts, giant cells, old bone	Dead of operation
26403	W F	Tibia, right			Central lesion	Curettement, Nov 26, 1917; irradiation (postoperatively) amputation, Oct. 17 1918		Dead 3 yr. after amputation
[illegible]	W M 50	Femur head			Destruction of acetabulum, head and neck of femur	Exploration, Coley's toxins	Malignant spindle cells, pleomorphic osteoblasts	Lost
23343	F	Tibia, upper			Central osseous destruction, slight formation of bone, periosteal reaction	Amputation, 1917		Dead 5 yr later
17932	W M [illegible]	Frontal bone	1½	Deafness, no definite trauma	Skull defect in frontal bone	Excision, February 1921	Mixed, spindle and round cells	Dead 8 mos. after operation

27909	N M 42	Tibia, lower	18	Trauma, tumor pathologic fracture		Amputation, April 8, 1921	Malignant spindle cells, pleomorphic osteoblasts	Well 6 yr later
27890	W M	Femur lower	22	Fracture December 1919	Central tumor with expansion and periosteal reaction	Amputation, Feb. 4 1921	Mixed, spindle and round cells	Dead 1 yr 7 mos later
27842	W F 17	Femur lower	3	Pain, tumor		Exploration, March 18, 1921; amputation, May 18, 1921; post-operative irradiation, July 27 1921	Malignant spindle cells, pleomorphic osteoblasts	Dead 3 mos. after amputation
27418	W M 19	Radius, lower	5	Pain, tumor		Tumor, preoperative irradiation; amputation arm, excision of pectoral muscles and glands, June 22, 1921		Dead same year
27300	W F 26	Humerus, upper		Tumor, pathologic fracture		Resection tumor, April 1901; exploration, June 5, 1901; amputation, June 7 1901	Malignant spindle cells, pleomorphic osteoblasts	Alive 3 yr after operation, lost
26919	F 35	Femur lower, tibia, upper fibula	21	Trauma, 3 yrs; tumor second trauma		Amputation, August, 1920	Mixed, round and spindle cells	Dead 4 mos. later
26477	W M 20	Tibia, upper	48	Pain, tumor		Exploration, January 1917 (followed by [illegible] serum); exploration, Aug 1920; amputation, Dec. 22, 1920	Round and spindle cells	Well nearly 9 yr after amputation
26448	W F 14	Tibia, upper left	16	Pain, tumor		Curettement, September 1920; amputation, October, 1920; cauterization, June, 1920	Large round cells with giant cells	Dead 10 mos. after amputation
26709	W M 19	Femur lower		Tumor trauma		Exploration, May 22, 1909; excision, July 4, 1909; amputation, Aug 5, 1909	Large round cells with giant cells	Well 18 yr., 4 mos. later
26612	W M 15	Fibula, upper	3	Pain, tumor pathologic fracture	Marked osseous bone destruction with pathologic fracture, tumor of soft part and slight formation of bone cortical expansion	None		Dead
26303	W M	Femur lower		Pathologic fracture		Two amputations		Dead 2 yr later from other causes
24966	W F 12	Femur lower	3	Trauma, pain, tumor		Amputation, Aug. 28, 1919	Malignant spindle cells, pleomorphic osteoblasts, osteoid tissue	Dead 6 mos. later
23401	W F 20	Femur lower left	48	Tumor trauma		Preoperative irradiation, excision, May 8, 1918; amputation, June 6, 1918		Dead 3 yr 5 mos. later
22109	W F	Femur lower			Destruction of lower end of femur; repair of fracture	Amputation and Coley's toxin, July 2, 1918		Dead 3 mos. later
19934	W M 18	Humerus, upper right	5	Trauma 5 mos tumor 1 mo		Amputation, Feb. 9 1918	Large spindle cells, pleomorphic osteoblasts	Dead 2 mos. later
18471	W M 21	Femur mid-part	2	Trauma, pain, tumor		Exploration, Nov 19, 1914; amputation, Dec. 2, 1914	Malignant spindle cells, pleomorphic osteoblasts giant cells	Dead 5½ mos. later
16188	W M 16	Tibia, upper	2	Tumor	Osseous destruction, periosteal roughening	Exploration, Jan. 8, 1913; excision, upper third of tibia, Jan. 13, 1913; amputation thigh, August, 1914	Mixed spindle cells, pleomorphic osteoblasts with giant cells	Dead 1 yr later
15404	W F 18	Tibia	4	Trauma with repaired fracture		Immediate amputation, Jan. 14 1914	Malignant spindle cells pleomorphic osteoblasts	Dead from operation

TABLE 22. OSTEOGENIC OSTEOLYTIC SARCOMA (Continued)

P. N.	Race, Sex and Age	Location	Duration, mos.	Symptoms	Roentgen Findings	Treatment	Microscopic Findings	Results of Treatment
14230	W F 24	Femur lower			Central destruction (aneurysm)	Amputation, June 2, 1913	Mixed spindle and round cells, pleomorphic osteoblasts, giant cells	Dead 11 yr later
13032	W M 29	Tibia, upper	24	Trauma, pain, tumor	Central destruction	Curettement, Aug 8, 1912; toxins and amputation, Sept 19, 1912	Mixed spindle and round cells	Dead 7 mos. later
13030	W M 25	Femur lower	8	Pain, tumor		Exploration, Jan 7 1911; amputation, Sept 22, 1911	Mixed spindle and round cells	Dead 8 days after amputation (toxemia)
11282	W M 60	Humerus, upper	17	Tumor, pathologic fracture trauma, pain		Amputation, July 24, 1911	Mixed spindle and round cells	Dead 6 mos. later
10868	W F 12	Femur lower	3	Pain, swelling		Coley's toxins; curettement, Sept. 27 1910	Large round cells	Dead 4 mos. later
10602	W M 30	Humerus, shaft	24	Pain, trauma, pathologic fracture	Central destruction	Curettement, Aug 23, 1910; curettement, Oct. 10, 1910; amputation, April, 1912	Mixed spindle and round cells, osteoid substance, giant cells	Dead 4½ yr after amputation
9726	W F 12	Femur lower				Amputation, May 31, 1909	Malignant spindle cells, pleomorphic osteoblasts, few giant cells	Dead 2 yr later
9307	W M 15	Tibia, head and shaft	3	Pain, tumor		Curettement; amputation 10 days later	Mixed spindle and round cells	Dead 3 mos. later
9073	W M 34	Ulna, upper	20	Tumor		Resection, May 12, 1907	Spindle cells, giant cells	Dead 2 yr later
8182	W M 41	Femur upper left	18	Limp, tumor	Osseous destruction	Exploration, May 2, 1907		Lost
7984	W F 17	Fibula, upper	9	Pathologic fracture, tumor pain	Complete destruction	Amputation, 1904	Malignant spindle cells, pleomorphic osteoblasts with giant cells	Dead 9 mos. later
6430	N M [illegible]	Femur lower		Pain, tumor		Exploration, May 29, 1903 amputation, July 6, 1903	Malignant spindle cells, pleomorphic osteoblasts	Lost
3880	W F 48	Tibia, upper	24	Pain, tumor		Exploration amputation, 1901	Malignant spindle cells, pleomorphic osteoblasts, giant cells	Well 2 yr., lost
3331	W M 30	Tibia, upper	11	Pain, tumor pathologic fracture		Amputation, Aug. 10, 1900	Malignant spindle cells, pleomorphic osteoblasts, with giant cells	Dead 2½ mos. later
3451	W F 16	Tibia, upper right	5	Pain, tumor repaired fracture		Exploration and amputation, 1899	Mixed spindle and round cells with giant cells	Dead 6 mos. later (pulmonary metastases and recurrence in stomach)
312	W M 22	Femur lower	7	Pain, tumor	Osseous destruction	Exploration, Feb., 1890 amputation May 1890	Mixed round and spindle cells	Dead 5 mos. after amputation

The distinguishing features in the roentgenogram, however are the melting away and perforation of the bone shell at an early stage in disease when the area of destruction is still asymmetrically located, the presence of a periosteal reaction (often with right-angle spicules) and the slight degree of cortical expansion In the benign cyst the bone shell is symmetrically expanded, and the zone of destruction traverses the whole diameter of the marrow cavity before a pathologic fracture leads to perforation of the bone shell. There is also, in most instances, definite indication of the formation of new bone on the inner border of the expanded cortex, a finding lacking in osteolytic sarcoma (Fig 155)

In advanced cases, the marked osseous destruction and periosteal involvement make the diagnosis of malignancy relatively certain. Metastatic carcinoma or a focus of multiple myeloma may then be suspected, but the bone has a more splintered and worm-eaten appearance and the degree of invasion into the soft parts is far more pronounced in osteolytic sarcoma. Usually the youth of the patient will aid in making the distinction since carcinoma and multiple myeloma are practically restricted to the years beyond 35 but it must be remembered that this form of sarcoma may also occur in later life

The more protracted cases of osteolytic sarcoma are puzzling These occur in adults and are nearly always confused with a benign giant-cell tumor The epiphysis is secondarily invaded by an expansile tumor with a perforated bone shell and a definite periosteal reaction (Fig 160) The metaphyseal portion of the bone is included in the destructive process, and in several instances the joint cavity has become secondarily involved because of erosion or splitting of the articular cartilage The history may extend over a period of from three to six years, and an operation, including exploration and biopsy is necessary to rule out a benign giant-cell tumor Cases of this type have been reported by Goforth, Finch and

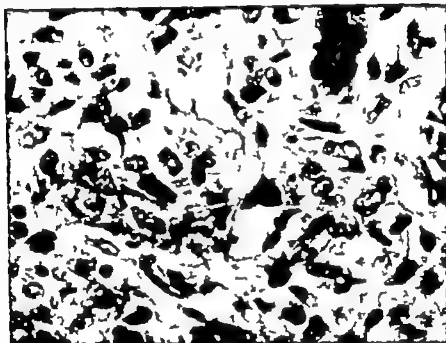


FIG. 152 (No. 39278) High-power photomicrograph of the tissue which is a mixture of malignant spindle and abortive osteoblasts.

Goforth, J L. Giant cell tumor of bone Arch. Surg. 13 846, 1926.



Fig. 153 (No 16158) Early roentgenogram of a case of osteolytic sarcoma in the upper end of the tibia of a white boy aged 16 taken two months after the onset of symptoms. The tumor was three times excised before amputation was performed. The patient died one year afterward. A small area of osseous destruction is shown in a subcortical and metaphyseal location perforating the cortex. The roentgenogram of the chest taken shortly before death shows a huge mediastinal mass on the right, overlapping the heart shadow



Fig. 154 (45124) Osteolytic, osteogenic sarcoma of the upper tibia. The lesion occurred in a patient of 16 years, who had symptoms of pain, fever and leucocytosis, suggesting osteomyelitis. The pain had been present for 7 weeks. (*Top*) Roentgenograms show an area of bone erosion which has spread through the cortex and has produced periosteal lipping on the side nearest the fibula. (*Bottom*) Photomicrograph shows the malignant character of the ossifying connective tissue



FIG. 155 (No 41194) Roentgenogram of an osteolytic sarcoma. The periosteal reaction, the perforation of the bone shell and the absence of osseous expansion led to the correct diagnosis from the roentgenogram The patient is well 15 years following amputation

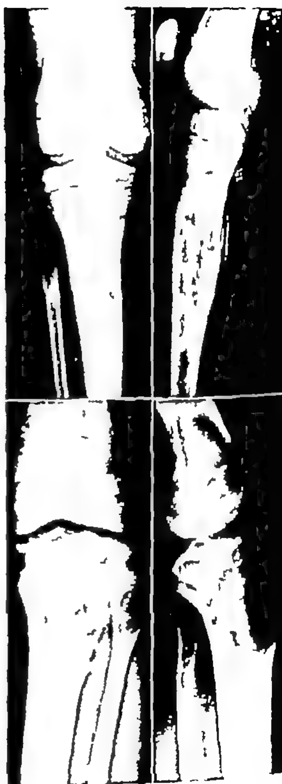


FIG. 156 (*Right*) Roentgenograms of two cases of osteolytic, osteogenic sarcoma involving the tibia. (*Top*) Roentgenogram in a case of a child, aged 11 with symptoms and an appearance simulating osteomyelitis.

(*Bottom*) Roentgenogram of an osteolytic osteogenic sarcoma in a boy of 17 The lesion suggests a benign giant-cell tumor except for the age and periosteal lipping

Gleave,* Chatterton and Flagstad,† and others as metastatic giant-cell tumor when the patients ultimately succumbed to metastases. A similar case recorded by Bloodgood‡ as a cure by amputation in this type of sarcoma has been classified by members of the Bone Registry as giant-cell tumor and its malignant nature doubted (Figs. 161 and 162)

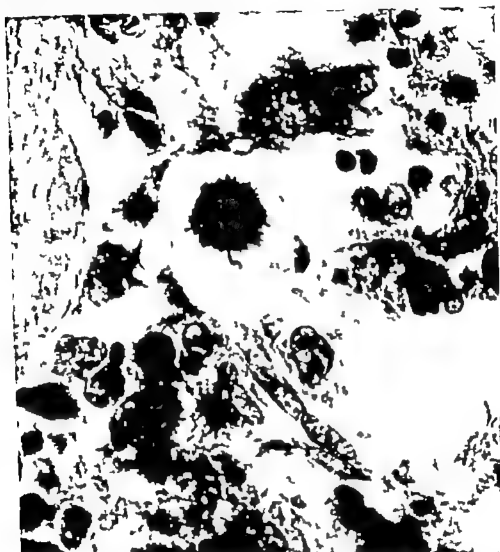


FIG. 157 (No. 41194) High-power photomicrograph showing the extreme anaplastic properties of the tumor cell in the case shown in Figure 143 Note the mitotic figure of the cell in the center of the field

The final diagnosis of these growths rests on a microscopic analysis and will be discussed in more detail subsequently when the histogenesis of this osteolytic form of sarcoma is considered.

GROSS PATHOLOGY

At exploration, a vascular tumorous mass may be found in the soft parts confined by muscle and fascia. More commonly the tu

* Finch E. F and Gleave H. H. A case of osteoclastoma with pulmonary metastases, J Path. & Bact. 29 399 1926.

† Chatterton, C. C., and Flagstad, A. E. Peculiar Behavior of Giant-Cell Tumors, J Bone & Joint Surg. 9 113, 1927

‡ Bloodgood, J C. The diagnosis and treatment of benign and malignant tumors of bone J Radiology 1 147 1920.

mor is beneath the periosteum with the bulk of the neoplasm within a shell of cortical bone. Vascularity is the rule, and a mass resembling a blood clot or active hemorrhage may be encountered (Figs. 151



FIG. 158 (No 86724) An osteolytic sarcoma occurring in a boy aged 10 who died of metastases despite an early operation The appearance in the roentgenogram is not unlike that of a cyst of the bone except that the areas of destruction are asymmetrically located and have extended up and down the shaft of the bone rather than across the medullary cavity

and 162) In one case (Fig 163) an exploratory incision, made under the impression that an abscess was present, gave rise to severe hemorrhage which resulted in a marked anemia. In most instances in which the operation opens up the medullary spaces of the cancellous bone, profuse bleeding occurs.

The neoplastic mass is soft and friable and usually resembles the blood-stained tissue seen in giant-cell tumor More fibrous areas, white and firm, are usually to be found, and where this more consistent material predominates, secondary hemorrhagic cysts are enclosed by it.

Amputated specimens show a mixture of fibrous and hemorrhagic tissue permeating the marrow cavity rupturing the cortex and spreading subperiosteally and into the soft parts. The site of the tumor is practically always to the shaft side of the epiphysis, and at this point the shaft is usually fractured transversely In early cases the cancellous bone is rapidly destroyed, and the cortex perforated. Before this perforation occurs, destruction in the medullary cavity proceeds rapidly until the pressure within the bone shell is relieved, after which the tumor proliferates into the less resistant soft parts. However with the continued growth under released pressure in the medullary cavity the cancellous bone is capable of partial defense and reacts with slight sclerosis.

The central origin of the tumor prior to its escape into the soft parts, is evident in the specimens by the perforation of tumor into the subperiosteal zones in diametrically opposed directions. In advanced cases the entire shaft of the bone may be substituted by white fibrous tumor tissue dotted here and there with hemorrhage (Figs. 163 and 164)

MICROSCOPIC FEATURES

The microscopic sections account for the extreme vascularity of the tumor Blood spaces usually without endothelial lining are prevalent in a tissue composed of plump malignant spindle cells and round abortive osteoblasts. Histologically an extreme degree of malignancy or anaplasia is shown by the nuclei in cells of the various types. Hyperchromatism and mitotic figures are prominent throughout most of the sections (Fig 157) A varying amount of osteoid intercellular material can be demonstrated.

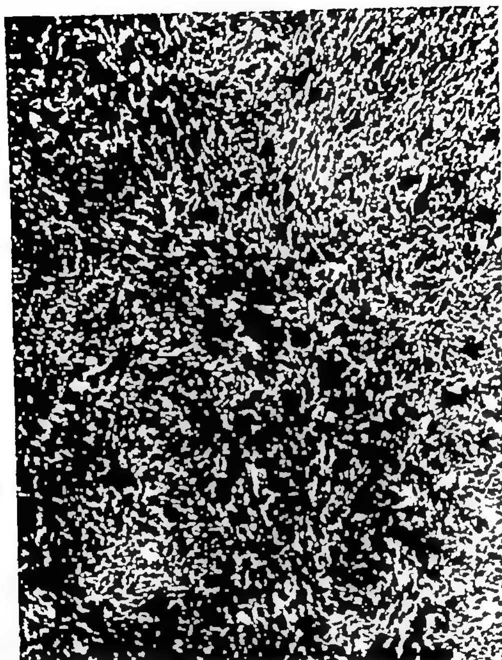


FIG. 159 (No. 36724) Photomicrograph showing early osteoblasts and spindle cells in osteolytic sarcoma. (Same case as Fig 158)



FIG 160 (No 40874) A secondary osteolytic sarcoma reported by Chatterton and Flagstad (J Bone & Joint Surg 9 113) as a metastatic giant-cell tumor occurring in a white woman, aged 30 who died eight years after the initial symptoms with pulmonary metastases. The roentgenogram depicts the unusual amount of osseous expansion caused by the tumor which has invaded the epiphysis

Often this preosseous material can be brought out only by special staining methods, but its definite tumorous origin is shown by its occurrence in metastatic pulmonary nodules.

Giant cells of the epulis type are common in the less rapidly growing neoplasms and are replaced by multinucleated tumor giant cells in the more malignant growths. The presence of these giant cells in the sections is often a source of confusion to pathologists and explains why some of the fatal cases of this form of osteolytic sarcoma have been reported as instances of metastasizing giant-cell tumor

The following are important points in the microscopic differential diagnosis (1) In the absence of infection, the finding of the malignant plump spindle cells with dusty nuclei is pathognomonic of sarcoma when the specimen under examination has been taken from bone, and particularly when these dusty nuclei are duplicated within the same cell. (2) The large round cells with numerous mitotic figures referred to here as abortive osteoblasts are also characteristic of malignancy (Figs. 168 and 169) These two malignant forms of spindle and round cells are common to osteolytic sarcoma of bone and are never found in the stroma of a uninfected benign giant-cell tumor The benign giant-cell tumor may have spindle and round cells in its stroma, but these are small and have not the malignant appearance in their nuclei that is seen in the round and spindle cells just described. (3) Giant cells are sparse in osteolytic sarcoma and rarely predominate in the section. They are small, usually have less than fifteen nuclei to the cell, and show a tendency to be replaced by giant cells of the malignant tumor type (Fig 170) In benign giant-cell tumors the giant cell predominates, and these cells average over fifteen nuclei.

The details of the microscopic appearance of these tumors are best obtained from the photomicrographs shown here. The relative frequency of giant cells in these tumors and the constancy of the findings of the malignant spindle cells or pleomorphic osteoblasts can be judged by referring to the microscopic notes recorded in Table 22.

It is important to call attention to certain features that set this tumor apart from other forms of sarcoma of the bone. Although in many of the tumors the malignant spindle cell rather than the osteoblast predominates, this neoplasm can be distinguished from periosteal fibrosarcoma by the failure of the early connective-tissue cells to differentiate into fibroblasts with whorl formation

fibrillae. Instead, they are converted into teoblasts of the type described. The small nounts of osteoid substance produced are t seen in fibrosarcoma.

Osteolytic sarcoma is distinguished micro-

tumor as a more malignant grade of sclerosing sarcoma. This point of view may be justified as a histopathologic interpretation. The roentgenologic and gross pathology however are so destructive that osteolytic



FIG. 161 (No. 14229) An osteolytic sarcoma arising secondary in a woman aged 61 who was cured by amputation. In the roentgenogram the sarcoma was differentiated with difficulty from a benign gaint-cell tumor but it has a more metaphyseal location and a definite periosteal reaction.

scopically from the sclerosing from by the scarcity of the osseous substance produced, and by the fact that the osteoblasts, instead of associating themselves with irregular spicules of newly formed bone tend to show extreme degrees of anaplasia and lie free in a stroma of spindle cells. There is, however a slight overlap, microscopically in an occasional case of the so-called early sclerosing type which is discussed under sclerosing osteogenic sarcoma. This overlap has led to the classification of this type of sarcoma deserves recognition as a separate form, from a practical point of view

Differentiation of this type of sarcoma from the chondral forms is easily made by the microscope as both calcifying cartilage, such as is seen in chondroblastic sarcoma, and myxoma and fetal cartilage such as are seen in chondromyxosarcoma, are lacking

The interpretation of this osteolytic neoplasm as an angiosarcoma is ruled out by the definite signs of ossification of tumorous origin seen in metastatic pulmonary



FIG. 160 (No. 40874) A secondary osteolytic sarcoma reported by Chatterton and Flagstad (J Bone & Joint Surg 9: 113) as a metastatic giant-cell tumor occurring in a white woman, aged 30 who died eight years after the initial symptoms with pulmonary metastases. The roentgenogram depicts the unusual amount of osseous expansion caused by the tumor which has invaded the epiphysis.

Often this preosseous material can be brought out only by special staining methods, but its definite tumorous origin is shown by its occurrence in metastatic pulmonary nodules.

Giant cells of the epulis type are common in the less rapidly growing neoplasms and are replaced by multinucleated tumor giant cells in the more malignant growths. The presence of these giant cells in the sections is often a source of confusion to pathologists and explains why some of the fatal cases of this form of osteolytic sarcoma have been reported as instances of metastasizing giant-cell tumor

The following are important points in the microscopic differential diagnosis (1) In the absence of infection, the finding of the malignant plump spindle cells with dusty nuclei is pathognomonic of sarcoma when the specimen under examination has been taken from bone and particularly when these dusty nuclei are duplicated within the same cell. (2) The large round cells with numerous mitotic figures referred to here as abortive osteoblasts are also characteristic of malignancy (Figs. 168 and 169) These two malignant forms of spindle and round cells are common to osteolytic sarcoma of bone and are never found in the stroma of a uninfected benign giant-cell tumor The benign giant-cell tumor may have spindle and round cells in its stroma, but these are small and have not the malignant appearance in their nuclei that is seen in the round and spindle cells just described. (3) Giant cells are sparse in osteolytic sarcoma and rarely predominate in the section. They are small, usually have less than fifteen nuclei to the cell, and show a tendency to be replaced by giant cells of the malignant tumor type (Fig 170) In benign giant-cell tumors the giant cell predominates, and these cells average over fifteen nuclei.

The details of the microscopic appearance of these tumors are best obtained from the photomicrographs shown here The relative frequency of giant cells in these tumors and the constancy of the findings of the malignant spindle cells or pleomorphic osteoblasts can be judged by referring to the microscopic notes recorded in Table 22.

It is important to call attention to certain features that set this tumor apart from other forms of sarcoma of the bone. Although in many of the tumors the malignant spindle cell rather than the osteoblast predominates, this neoplasm can be distinguished from periosteal fibrosarcoma by the failure of the early connective-tissue cells to differentiate into fibroblasts with whorl formation

of fibrillae. Instead, they are converted into osteoblasts of the type described. The small amounts of osteoid substance produced are not seen in fibrosarcoma.

Osteolytic sarcoma is distinguished microscopically from the sclerosing from by the scarcity of the osseous substance produced, and by the fact that the osteoblasts, instead of associating themselves with irregular spicules of newly formed bone, tend to show extreme degrees of anaplasia and lie free in a stroma of spindle cells. There is, however, a slight overlap microscopically in an occasional case of the so-called early sclerosing type, which is discussed under sclerosing osteogenic sarcoma. This overlap has led to the classification of this type of tumor as a more malignant grade of sclerosing sarcoma. This point of view may be justified as a histopathologic interpretation. The roentgenologic and gross pathology, however, are so destructive that osteolytic sarcoma deserves recognition as a separate form, from a practical point of view.



FIG. 161 (No. 14229) An osteolytic sarcoma arising secondary in a woman, aged 61, who was cured by amputation. In the roentgenogram, the sarcoma was differentiated with difficulty from a benign gaint-cell tumor, but it has a more metaphyseal location and a definite periosteal reaction.

Differentiation of this type of sarcoma from the chondral forms is easily made by the microscope, as both calcifying cartilage, such as is seen in chondroblastic sarcoma, and myxoma and fetal cartilage, such as are seen in chondromyxosarcoma, are lacking.

The interpretation of this osteolytic neoplasm as an angiosarcoma is ruled out by the definite signs of ossification of tumorous origin seen in metastatic pulmonary

nodules. The large malignant osteoblasts are not the type of cell seen in hemangiomas that undergo malignant change.

HISTOGENESIS

A study of the gross specimens and the roentgenograms in the cases of osteolytic sarcoma readily confirms the conclusion that this tumor at its time of origin and in its early phases is confined to the medullary or cancellous structures within the space encircled by the cortical layers of the bone.* Microscopic evidence supports the view that the neoplasm represents an early phase of osteogenesis via fibrous tissue. The spindle cells, although showing many signs of pleomorphism and malignancy differentiate into osteoblasts of an abortive variety. The tendency toward the production of bone is indicated by the small amounts of osteoid tissue which can be found even in the metastatic pulmonary nodules. In tracing the histogenesis of this tumor therefore, it is necessary to account for the central origin of the osteogenesis and to seek an explanation for the failure of the process to achieve the formation of fully developed new bone and to cause, instead, osteolysis.



Fig. 162. (No. 14229) The gross specimen shown is characteristic of the old pathologic entity of malignant aneurysm of the bone. The microscopic structure of the tumor was typical of the osteolytic form of osteogenic sarcoma. (Same case as Fig. 161.)

The answer is to be found in the type and localization of the connective tissue from which this neoplasm takes its origin. This tissue is the endosteum of the bone and is concerned in the formation of the cancellous bone that follows the resorption of calcified cartilage.

* A variant of sclerosing sarcoma resembling these tumors microscopically and arising beneath the periosteum is described in Chap. 8.

Fig. 163 (No. 28498) Roentgenograms of a case of an early osteolytic, osteogenic sarcoma of the tibia. The roentgenograms show cancellous and cortical bone being eroded, without expansion of the bony shell.



Fig 164 (No. 36456) A late stage of osteolytic sarcoma simulating metastatic carcinoma. The patient was an adult, aged 39 who died three years after the amputation. (A) shows the destruction of the shaft of the bone by the new growth producing a pathologic fracture Osseous expansion is not marked. (B) emphasizes the white fibrous nature of the tumor substance invading the shaft above the epiphysis.



FIG. 165 (No 36456) Low-power photomicrograph showing the central location of the tumor mass depicted in Figure 164. The surviving trabeculae of cortical bone are enclosing the neoplastic tissue

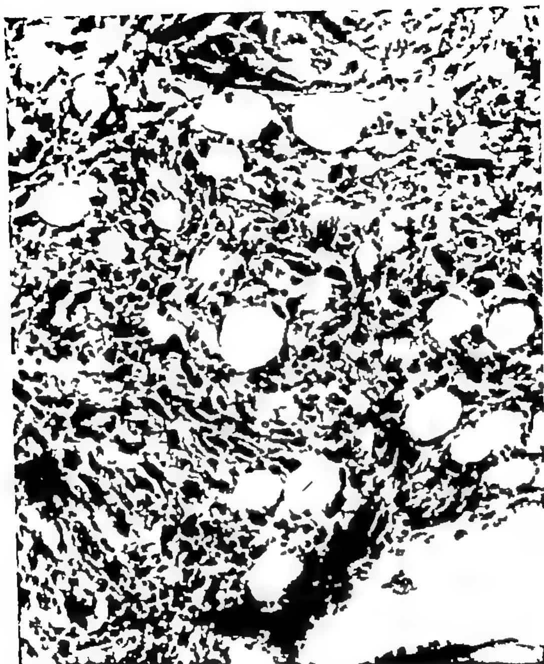


Fig. 166 (No. 36456) High-power photomicrograph of the tumor shown in Figures 164 and 165 Malignant spindle cells and osteoblasts are invading the fatty bone marrow

In human embryos from 90 to 140 mm., the sections of the long bones show an early cartilaginous stage in the regions of the epiphysis and the metaphysis, but throughout the diaphysis of the bone ossification is in progress. At this stage the cortex is being re-formed, perforated by channels of the future haversian system and the cartilage at the center of the bone is being resorbed to create a vascular cavity Osteogenic tissue is visible on both sides of the cortex, the outer layer constituting the periosteum and the inner layer the endosteum. At this stage ossification progresses rapidly in the metaphyses within the surrounding endosteum. Newly formed vessels are prominent, and spindle cells and round cells of the osteoblastic type are abundant, a picture not unlike that seen in osteolytic sarcoma. The important point is that endosteal ossification following in the wake of calcified cartilage occurs in a tissue composed of a mixture of round and spindle cells and new blood vessels, presenting an appearance similar to osteolytic sarcoma (Fig 173) This process, it is believed, is



FIG. 167 (No. 28574) Photomicrograph showing the formation of blood spaces rimmed by giant-cells found in the vascular areas of osteolytic sarcoma.

different from the direct membranous ossification that occurs after the periosteum has become more highly differentiated. It is more rapid, cellular and vascular It is to be inferred, therefore, that the osteolytic sarcoma arises in ossification of this endosteal type and its cellular and hemorrhagic character is a constant accompaniment of this primitive postcartilaginous formation of bone

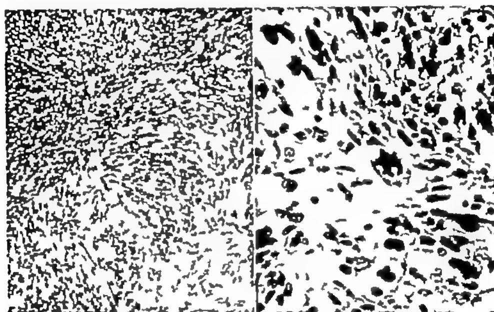


FIG. 168. (No. 38882) Low and high-power photomicrograph showing the hyperchromatism and pleomorphism associated with the osteolytic type of osteogenic sarcoma occurring in patients under 30 years of age The low power photomicrograph emphasizes the connective-tissue origin of the neoplasm the high-power its tendency to differentiate into osteoblasts.

The failure of the osteolytic type of sarcoma to produce adult bone is to be ascribed to the dependence of ossification in this type of tissue on the presence of calcified cartilage undergoing resorption While in the embryo the entire core of the future bone provides such a warehouse of cartilage for the storage of calcium after birth, at the age periods when osteolytic sarcoma occurs, no such adequate supply of calcified cartilage is available. The preosseous cellular tissue in the sarcoma readily outstrips the formation of osseous substance The vessels accompanying this endosteal proliferation may be a factor in eroding the structures of the bone, but in all probability the sarcomatous tissue itself enclosed within the cortical layers may be responsible for pressure atrophy which in turn opens up numerous vascular channels in the medullary cavity or the tumor tissue may elaborate a lytic substance

The majority of cases of osteolytic sarcoma arise within cancellous bone in the metaphyseal region in patients under 20 which seems to indicate that the neoplasm has its source in a normal growth process concerned in the development of cancellous bone in its metaphyseal region during puberty The normal growth impetus underlying this sarcoma, when it occurs in young patients, accounts in part for the poor prognosis.

There is, however another group of osteolytic sarcomas that are histologically of the same type and that occur in patients over 30, in whom the outlook is not so grave and in whom the duration of symptoms dates back not months but years. The question arises Is there a secondary form of

osteolytic sarcoma which follows on some benign chronic condition and which would thus explain this more protracted clinical picture? This question is intimately connected with the problem of so-called metastasizing giant-cell tumor and in some of these cases of metastatic giant-cell lesions period of 25 years and ultimately give rise to osteolytic sarcoma. In some cases localized areas of Paget's disease or an old fracture may give rise to such a secondary malignant growth. All of the patients in this series over 30 years of age have been examined carefully from this

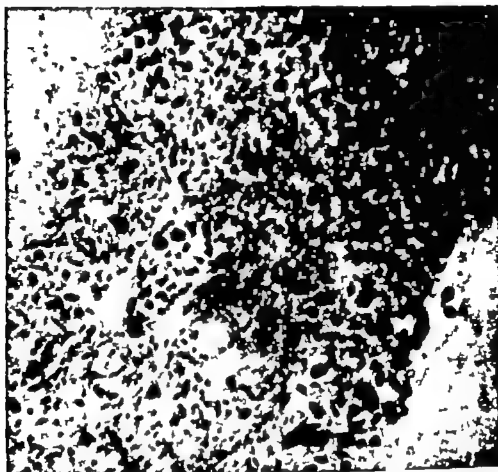


FIG. 169 (No 41194) Photomicrograph showing the malignant pleomorphic cells referred to as abortive osteoblasts. Note the vascular spaces associated with the clinical features of aneurysm of the bone.

the possibility that a secondary sarcoma arose at the site of an unhealed benign lesion must be seriously considered.

We have seen two cases in one of which a benign giant-cell tumor microscopically verified, healed imperfectly and four years later was the site of osteolytic sarcoma (microscopically verified) In the other instance, there was adequate roentgen evidence of accompanying fibrous dysplasia which was fractured repeatedly over a standpoint. In about one-third of the cases a history of a preceding osseous lesion was recorded. In two cases a preceding fibrous dysplasia of bone was present for 15 or 25 years.

The important phases of these supposedly secondary osteolytic sarcomas, regardless of their etiology concern the clinical course and ultimate result. As is brought out in the discussion of prognosis and treatment, elderly patients with this

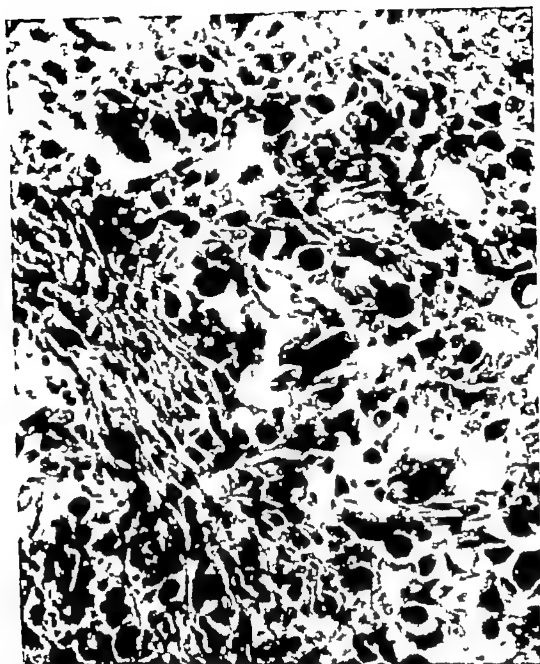


FIG. 170 (No. 36724) Photomicrograph showing the tendency of small giant cells of the epulis type to be associated with malignant tumor giant cells in osteolytic sarcoma. The small giant cells of the epulis type are intermingled with spindle cells and early osteoblasts. The roentgenogram of this case is shown in Figure 158.

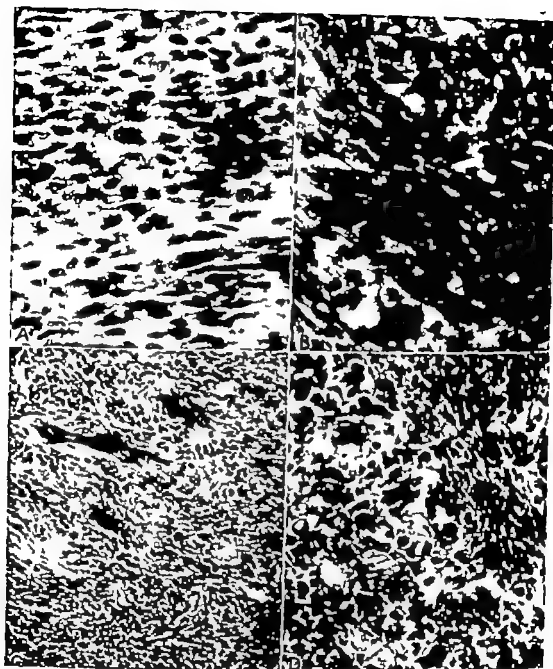


FIG. 171 Photomicrographs showing the histogenetic cycle in osteolytic sarcoma. (A) shows malignant spindle cells predominating. The nuclei are large and vesicular. Mitotic figures are frequent. (B) shows a structure of malignant spindle and round cells. Abortive osteoblasts predominate. (C) depicts small osteoblasts associated with imperfect bone formation. This section was taken from a metastatic pulmonary nodule and shows more osteoid substance than is usually found in these new growths. (D) pictures a predominance of abortive osteoblasts intermingled with an imperfect osteoid substance which is being resorbed by small giant cells.

lition are more apt to be permanently
·d by radical operation and even if
ıg of metastasis may have a postopera
duration of life exceeding five years.

PROGNOSIS AND TREATMENT

·f 121 cases of osteolytic sarcoma fol
ed more than five years, those in which

the patients were treated by irradiation either preoperatively or postoperatively without effect, nor did erysipelas and prodigiosus toxins (Coley's) in the five cases in which they were used affect the outcome. The duration of the symptoms in the cured cases was usually over 18 months and averaged over 4 years. This is remark

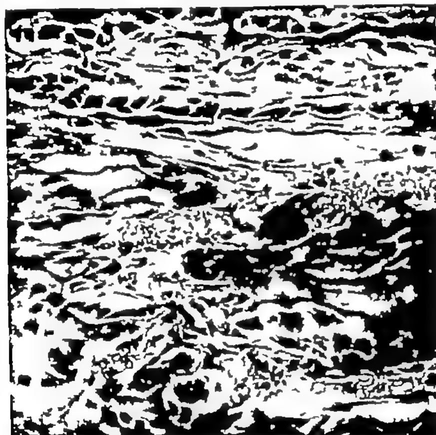


FIG. 172. Cancellous bone formation in a human embryo of 150 mm. The mixture of hemorrhage, giant cells, spindle cells, and osteoblasts among the bone spicules shows the same combination of cellular elements found in osteolytic sarcoma arising in cancellous bone

e patient may be considered as perma
ntly cured, that is, living beyond five
ars, number only 19 or about 16 per cent
the total. All these patients except two
ere treated by amputation, usually fol
wing an exploratory operation after one
more weeks. In one case resection of
e tiba was performed, followed by im
anting of a graft from the opposite fibula.
ı the other the radius was resected.
ı the cases terminating fatally four of

able, because most of the patients with this form of sarcoma are between the ages of

TABLE 23. OSTEOLYTIC OSTEOGENIC SARCOMA

Total Number of Cases	149
Total followed cases	131
Living under five years	10
Total fatal cases	102
Cases well over five years	19
Per Cent five-year cures	16

10 and 20 years and give a history of symptoms of less than one year

In regard to the curability of this form of osteolytic sarcoma, one must conclude that only when amputation is employed can favorable results be achieved. Even in sections showed many giant-cells. This mistaken diagnosis also was made in one of the cases placed among the five-year cures.

In the youngest patients, the duration of life after treatment approximates the duration of symptoms before examination. In



FIG. 173 Higher magnification from the same embryo shown in Figure 172. This picture emphasizes mixed spindle and round cells, in an area of hemorrhage. The bone spicule in the center of the picture is being resorbed.

such cases there is a possibility that while the patient will live over five years after operation he may ultimately succumb to metastases. There are four elderly patients in this series who lived from five to seven years after operation but who finally died with pulmonary metastases. These four cases have not been included in the five-year cures although possibly they are entitled to consideration as such and would raise the per cent of five-year cures to 19 In each instance the initial diagnosis was a benign giant-cell tumor and the original this series the symptoms average eleven months and the postoperative duration of life an equal period. The prognosis in the chronic forms of osteolytic sarcoma in adults is much better and supports the inference that the more readily curable cases are secondary to some preceding benign lesion. In cases in which the upper femur or humerus is involved, no cures are recorded. External irradiation should be tried. In two recent cases treated in this fashion, one in a girl, the other in a man over 50, life was prolonged beyond three years al-

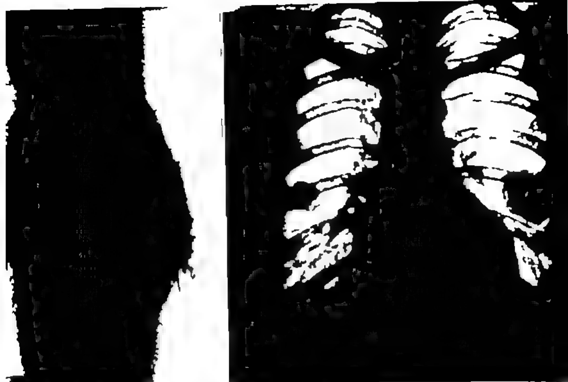


FIG. 174. Roentgenograms of a patient who lived four years following amputation for osteogenic sarcoma of the femur in spite of chest metastasis. The leg was amputated on February 14, 1940. Metastasis to the left chest appeared in March, 1941. The patient died in March, 1944. He was bedridden in April, 1941, but regained his health and stayed apparently well for more than 2 years on dicalcium phosphate with viosterol and stilbesterol, 2½ mg. daily.



FIG. 175. Roentgenograms showing the progression of an osteolytic, osteogenic sarcoma of the lower femur in a man of [illegible]. The lesion was treated by irradiation and oral estrogen and calcium therapy beginning in October, 1940. The lesion was considered inoperable when first seen. The patient died in February, 1946, with extensive pulmonary metastases. He had several years of comfort on the calcium and estrogen therapy.



FIG. 176. Roentgenograms of humerus and chest in a case of osteogenic sarcoma in a woman of 36. The tumor was explored in August, 1937 and unsuccessfully irradiated. In June, 1938 the humerus was resected. In January 1939 there was local recurrence and extensive metastases to the chest. Under oral estrogen and calcium therapy the metastases in the chest ossified and the patient coughed up several metastases, from 1 to 2 cm in diameter of eburnated bone. She died of strangulation from one of these metastases on October 13 1939

though cure was not effected. This treatment is of benefit when amputation is refused. It may be reinforced by estrogen and calcium therapy (see Chap. 8, p 207)

In a group of patients who refused operation or in whom the lesion was inoperable, the authors have used oral estrogens and calcium as a palliative treatment for the forms of osteogenic sarcoma. No benefit has been observed in three cases of chondrosarcoma. In two cases of sclerosing osteogenic sarcoma of the sacrum and ilium, respectively beneficial results were insignificant. In the three cases illustrated here, definite symptomatic improvement occurred. The patients were maintained in an ambulatory condition and it was thought that life was prolonged.

SUMMARY

The osteolytic form of osteogenic sarcoma is a destructive tumor arising in the region of the marrow cavity in the shaft of the long bones. Clinically the tumor which usually comes under treatment after about one year of symptoms, shows a wide age distribution, being most frequent in young adults and becoming gradually less frequent with advancing age. The neoplasm shows an unusual tendency to produce a pathologic fracture. In the roentgenogram a central area of rapid bone destruction which dissolves the cortex without expansion and with definite periosteal involvement can be seen.

This type of tumor is related histogenetically to the formation of cancellous bone from the endosteum which normally follows in the wake of calcified cartilage. Since sufficient amounts of this calcified cartilage are absent at the site and the age when these tumors arise, ossification is incomplete and an osteolytic tumor is the result. Microscopically this is characterized by large malignant spindle cells and round

osteoblasts with numerous mitotic figures and a small amount of poorly formed intercellular osteoid tissue. The giant cells present in the lesion may represent an attempt on the part of these cells to remove the incompletely formed osteoid tissue. In these cases early amputation or radical resection was found to offer the best chances for a permanent cure. All the cases (16 per cent) of five-year cures in this group of tumors were achieved by this method. An examination of these cured cases shows that half of them presented exceptional features, in that they occurred in patients over 30 with a long duration of symptoms suggesting that the sarcoma was secondary to some preceding chronic and benign lesion External irradiation is an effective form of palliative treatment.

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10

Tumors Related to Growth Subsequent to Chondrification—Bone Cysts

No lesions of the bone have been accorded such a varied pathologic interpretation as osteitis fibrosa (cystic disease) and giant-cell tumor

When bones grow their mineralized content undergoes replacement. This process is conspicuous when calcified cartilage is replaced by cancellous bone or when the latter is replaced by compact bone. This resorptive phase, which is character ized by a proliferation of vessels and giant cells (angiospongiosa) produces a temporary loss of structure in the microscopic zone where it occurs. An exaggeration of it results in macroscopic cavitation of the bone such as is seen in bone cysts and giant-cell tumors

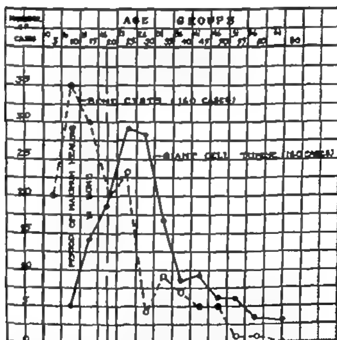


CHART 8. Age distribution of bone cysts and giant cell tumors. As the frequency of cysts decreases, that of giant-cell tumor increases.

Thus, there are reasons to consider both giant-cell tumor and osteitis fibrosa as pathologically related, particularly because of the number of cases combining the histologic characteristics of both.

In the ensuing chapters evidence supporting the kinship of giant-cell tumor and

phases of osteitis fibrosa is presented, and the normal developmental processes under lying these lesions are emphasized.

CLINICAL FEATURES

The conception of osteitis fibrosa has been widely extended since the time of von Recklinghausen* to include a multiplicity of lesions. The solitary bone cyst, which is a form of osteitis fibrosa found usually in the shaft of the long bones of young adults, is clinically the most frequent, and pathologically the outstanding representative of this group. Among the other diagnostic categories separated from the rather broad and ill-defined classification of osteitis fibrosa are diffuse cystic disease associated with hyperparathyroidsim, generalized and monosteotic fibrous dysplasia. These will be considered subsequently

Von Mikulicz and Bloodgood† were among the first to observe that the age of a patient with a typical bone cyst is usually less than 21, and Silver‡ in his review of 97 cases in 1912, found only 18 patients who were past the age of 20 In 275 cases of bone cysts, the average age of the patients is between 10 and 15 although in about 20 per cent the patients are more than 21. This age distribution is one of the outstanding clinical features of the disease (Fig. 172)

The large majority of solitary bone cysts are confined to one of three favorite sites, the upper shafts of the femur humerus or tibia. In Silver s‡ table of 97 cases, the tumor was found in the femur in 31, in the humerus in 25 and in the tibia in 15 Elmslie§ was impressed that the upper part of the femur and the upper part of the humerus were the prevalent locations. The fig

BONE CYSTS

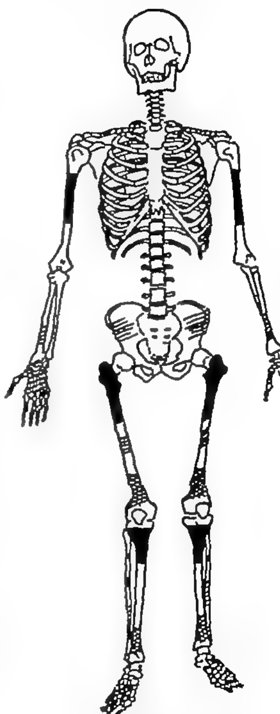


FIG. 177 Incidence of bone cysts according to skeletal location. The solid black areas indicate the most frequent sites the checked areas, the common sites and the diagonal lines, the locations occasionally involved. The bones in white are rarely affected. Note, the epiphyseal ends are not affected by solitary cysts.

* Von Recklinghausen. Die Fibrose oder deformierende Osteitis, die Osteomalacie und die osteoplastische Carcinose Festschr zu Rudolf Virchow 1891.

† See Bibliography at end of Chapter

‡ Silver D The so-called benign cyst of the bones, Am. J Orthop. Surg. 9 563 1912.

§ Elmslie R. C. Fibrocystic diseases of the bones, Brit. J Surg. 2 17 1914

TABLE 24 TYPICAL BONE CYSTS

Pathologic No	Race	Sex	Age	Location	Duration mos.	Symptoms	Treatment	Results of Treatment
62766		M	8	Femur inter trochanteric region	6	Pain	Curettage	Well 3 yr
62602		M	14	Maxilla an terior area	24		Curettage	Well 4 yr
62598	W	M		Radius	½	Trauma	Curettage	Well 4 yr
62590		M	7	Humerus, left	12	Fracture	Irradiation	Well 4 yr
63092	W	F	9	Humerus		Fracture		Well 2 yr
63068	W	M	18	9th vertebra	3			Well 2 yr
63140	W	F	4	Humerus		Fractures		Well 16 mos.
62348	W	M	36	Femur neck	216	Trauma		Lost
62244	W	M	12	Tibia, upper end	18	Pain		Lost
62118	W	M	4	Femur inter trochanteric region		Pain	Irradiation	Well 6 yr
62112		M		Femur greater trochanter	51	Pain	Excision	Well 6 yr
62064		M	8	Femur middle third		Fracture	Curettage	Well 7 yr
62034	W	M	9	Femur lower end		Tumor pain	Curettage	Well 7 yr
62022	W	M	16	Femur inter trochanteric region	3	Pain	Curettage	Well 8 yr
61826	W	M	47	Multiple	24	Pain	Curettage	Well 7 yr
61700	W	M	15	Humerus, upper end		Fracture	Curettage	Well 2 yr
61640	W	M	20	Femur greater trochanter		Trauma	Curettage, irradiation	Well 7 yr
61522	W	M	23	Tibia, upper third	24	Trauma	Curettage	Well 8 yr
61496	W	M	13	Humerus, upper	3	Weakness	Curettage	Well 8 yr
61474	W	F	11	Fibula upper metaphysis	sev	Pain	Curettage	Lost
61316	W	F	19	Ilium		Pain	Curettage	Lost
61182	W	F	26	Tibia, middle third	6	Pain	Curettage	Well 8 yr
61104	W	M	8	Humerus, neck		Fracture, recurrent	Curettage	Well 8 yr
60370	W	M	7	Tibia, upper end		Trauma	Curettage	Lost
60068	W	F	24	Mandible, body	144	Tumor	Curettage	Lost
60046	W	M	13	Humerus, upper metaphysis		Trauma	Curettage	Lost
59036	W	F	7	Left femur		Fracture	Curettage	Lost
58830	W	F	4	Femur neck			Curettage	
58662	W	F	11	Tibia, upper		Trauma	Curettage	Well 2 yr
58200	W	F	40	Humerus, neck		Trauma	Curettage	Lost
58186	W	M	21	Humerus, left		Fracture	Curettage	Well 11 yr
57878	W	F	28	Femur greater trochanter	216	Trauma	Curettage	Well 10 yr
57696	W	M	20	Ischium		None	Curettage	Well 12 yr

TABLE 24 TYPICAL BONE CYSTS (*Continued*)

Pathologic No	Race	Sex	Age	Location	Duration mos.	Symptoms	Treatment	Results Treatme
57536	W	F	8	Humerus, neck		Fracture		Lost
57220	W	M	15	Tibia, lateral condyle	12	Pain	Irradiation	Well 12 y
57184	W	F	14	Radius, lower third		Fracture	Curettage	Lost
57136	W	F	7	Femur neck	9	Limp		Well 12 y
56586	W	M	14	Humerus, upper shaft		Trauma		Well 12 y
56146	W	F		1st metatarsal	3	Tumor		Well 13 y
55620	W	M	12	*Femur upper*	[illegible]	*Pain*	*Excision*	
55082	W	F	15	Tibia	1	Pain	Irradiation	Well 2 yr
55722	W	M	6	Humerus, upper metaphysis	18	Trauma		Lost
54916	W	M	37	Tibia upper end		None		Lost
54662	W	M	17	Humerus, mid shaft		Fracture		Well 13 y
54894	W	F	4	Humerus, upper	18	Pain	Curettage	Well 5 yr
54568		M	10	Humerus, upper		Fracture	Immobilization	Dead 3 y
54046	W	M	11	Proximal phalanx, great toe	42	Trauma	Excision	Lost
53972	W	F	23	Tibia	30	Deformity	Irradiation	Well 2 yr
53578	W	M	19	Femur	36	Pain		Well 14 y
53410		M	40	Ulna		None		Lost
53238	W	M	60	Clavicle		Fracture	Excision	Lost
52850	W	M	57	Ilium, right	6	Pain		Well 16 y
52666	W	F	9	Tibia		Trauma	Curettage	Well 13 y
52456			15	Mandible	48	Trauma, tumor		Lost
52256		M	15	Multiple		Trauma		
51750		M		Humerus		Trauma		
51586	W	M	23	12th rib		None		Well 15 y
49960	W	M	32	Radius	12	Trauma		Lost
49732	W	F	11	*Tibia, shaft*	*0*	*Trauma, pain*		Well 15 y
49468	W	M	60	Femur neck	1	Pain		
49294	W	F	6	Ischium		Pain		Lost
48866	W	M	10	Tibia	11	Trauma	Curettage cautery	Lost
48156	W	M	24	Femur	1	Pain	Curettage	Well 5 yr
48318	W	M	8	Humerus		Repeated fractures		Lost
48262	W	M	24	Rib third		None	Resection	Well 15 yr
48138	W	M		Humerus, head	120	Pain		
47286	W	M	4	Humerus	18		Surgery irradiation	Well 6 yr
46182	W	F	36	Tibia	11	Pain	Curettage	Well 6 yr
46178	W	F	15	Femur	24			
46016	W	M	23	Femur	[illegible]	Fracture	Irradiation	Well 8 yr
45736	W	M	12	Humerus	1½	Pain	Curettage	Well 2 yr
45503	W	M	16	Foot, femur			Surgery	Well 8 yr
45133	W	F	13	Tibia			Irradiation	Well 6 yr
44794	W	F	14	Os calcis	24		Excision	Well 7 yr
44800	W	F	30	Tibia	28		Surgery	Well 10 yr

TABLE 24 TYPICAL BONE CYSTS (*Continued*)

Pathologic No	Race	Sex	Age	Location	Duration, mos.	Symptoms	Treatment	Results of Treatment
44552	W	M	10	Humerus			Irradiation	Lost
44140	W	F	14	Tibia	24		Curettage	Well 3 yr
44218	W	M	4	Femur			Irradiation	Well 7 yr
44102	W	M		Bone			Surgery	Well 8 yr.
43772	W	M	18	Humerus				Lost
44100	W	M	8	Femur	4		Irradiation	Well 7 yr
43718	W	M	35	Humerus			Irradiation	Well 8 yr
43160	W	M	15	Femur	[illegible]		Irradiation	Well 8 yr
43022	W	M	31	Tibia	1½		Curettage	Dead 6 mos
42040	W	M	[illegible]	Femur			Biopsy irradiation	Well 10 yr
41724	W	F	8	Humerus	[illegible]		Surgery	Well 8 yr
42526	W	M	15	Tibia	2		Irradiation	Well 6 yr
42438	W	M	12	Humerus	0			Lost
42304	W	M	39	Femur	4		Irradiation	Well 11 yr
44206	W	M	10	Humerus	3 da. injury			Well 7 yr
41374	W	M	3	Femur	2			Well 11 yr
40812	W	F	6	Multiple bones			Parathyroidism	Lost
40646	W	M	16	Shoulder				Well 8 yr
40230	W	M	10	Femur	12		Surgery	Well 12 yr
40124	W	F	16	Humerus	7		Surgery	Well 12 yr
40255	W	F	12	Femur				Well 12 yr

ures in our series are in accord with the observations of these authors. In 230 cases of solitary bone cysts, 77 were in the femur 68 in the humerus and 45 in the tibia. The fibula is next in frequency with 9 lesions. Of the cysts in the femur the majority were present in the upper end, most of these being in the region of the greater trochanter In the humerus, lesions in the upper end predominate, while in the tibia there is a similar predilection for the upper end. In all, about 75 per cent of these lesions show a metaphyseal location in these three bones (Fig. 177)

In these bones when the lesion is not near the epiphysis on the shaft side, the disease has extended over a sufficient number of years to allow migration toward the midshaft region, as the bone grows. But where these lesions usually occur and at the prevalent age period there is a relationship to an unossified epiphyseal line. An area of new bone in a metaphyseal region is involved, and the pathologic process appears to be related to this new bone formation. In the histologic study such a relationship can be definitely traced.

Clinically the patient comes under observation most frequently because of pathologic fracture. This is recorded in 45 per cent of the histories. The other clinical features of the bone cyst are swelling, slight deformity or a moderate degree of pain. Unless an injury resulting in fracture has been superimposed, the clinical history is not striking The average duration of symptoms is 2½ years. In about one-fifth of the cases the duration averages 10 years, the extremely chronic histories dating back from 20 to 40 years. The long latent period preceding diagnosis accounts for the occurrence of bone cysts in patients more than 20 years of age Here the lesion which arises in childhood is discovered late in life, as the consequence of some clinical incident leading to a roentgen examination, the

previous presence of the tumor remaining unsuspected because of the absence of symptoms. This is the so-called latent bone cyst.

In about one case out of ten gradually increasing deformity in either a single or several bones will be observed. These cases rarely have a solitary bone cyst, but instead show a diffuse involvement more properly termed fibrous dysplasia or fibrocystic disease of von Recklinghausen. While these cases embrace features typical of the solitary bone cyst, they are often associated with a general systemic affection (parathyroidism) and will be considered separately below

In clinical diagnosis it is important to bear in mind the variety of types included in the classification of osteitis fibrosa. The first type, the solitary bone cyst, is discovered in a patient between the ages of 5 and 15 in the metaphysis of the upper humerus, femur or upper tibia (Fig. 179) usually following a pathologic fracture. A second and very similar form of lesion (Fig. 180) is the more acute bone cyst of not more than six months duration, which borders directly on the epiphyseal line on its shaft side and contains histologically giant-cell areas. This is often mistaken *clinically* especially in the upper femur for a giant-cell tumor * In a third group of cases the cyst is of the latent type (Fig 181) The patient is older the symptoms of longer duration, the location is more apt to be in the region of the midshaft, and the bone near the defect is strengthened by thickening of the walls of the cavity In the smallest and last group of diffuse fibrocystic disease (Fig 182) there is a generalized involvement of one or more bones and a bending deformity The shafts of any of the long bones may be affected as well as the flat or small bones, the age is variable, and some complicating



FIG. 178. (Nos. 35233 34174 and 37798) Roentgen pictures of typical bone cysts in the localities most frequently affected. (A) *upper part of tibia, (B) upper part of femur and (C) upper part of humerus.* The lesions are near or at the metaphysis, and the ununited epiphyses in (A) and (C) indicate the youth of the patients. A pathologic fracture is shown in the upper part of the humerus.

* These more acute bone cysts are in reality a transitional lesion related to the giant-cell tumor and are described in detail under a separate heading.

TABLE 25 TYPICAL BONE CYSTS (*Continued*)

Path No	Race	Sex	Age	Location	Symptoms	Roentgen Findings	Treatment	Microscopic Appearance	Results of Treatment
25342	W	F	17	Tibia	Tumor 13 years	Cystic, bending	Resection	Typical osteitis fibrosa	
25343	W	M	17	Humerus, upper	Fracture	Encapsulated cyst			Well 3 years
25109	W	F	2	Tibia, lower third	Deformity fracture	Fracture, rarefaction	Excision	Typical osteitis fibrosa	Well 9 years
24818	W	M	4	Femur upper	Fracture	Cyst with fracture			Well 3 years
24748	W	F	16	Femur lower	Trauma, 9 years	Cystic, expansion	Excision	Typical osteitis fibrosa	Well 3 years
24098	W	F	24	Tibia, shaft	Tumor 10 years	Expansion, encapsulation	Excision	Typical osteitis fibrosa	Well 3 years
24000	W	M	5	Femur upper	Trauma, 20 months	Cystic, expansion			Well 1 years
23817	W	M	12	Femur upper	Fracture	Cystic, expansion	Curettage	Typical osteitis fibrosa	Well 8 years
21101	W	M	23	Radius, lower	Tumor 10 years	Cystic, expansion	Curettage	Typical osteitis fibrosa	Well 10 years
20996	W	F	28	Tibia, lower	Tumor 8 years	Cystic, expansion	Excision	Typical osteitis fibrosa	Well 4 years
20500	W	F	14	Femur upper	Tumor		Incision	Typical osteitis fibrosa	Well 5 years
20848	N	M	35	Femur shaft	Tumor, 8 years	Cystic expansion	Amputation	Typical osteitis fibrosa	Well 7 years
19557	W	M	8	Tibia, upper	Tumor	Cystic, expansion	Curettage	Typical osteitis fibrosa	Well 4 years
17432	W	F	12	Radius, lower	Tumor	Cyst with fracture			
16454	W	F	5	Tibia, lower	Tumor 2 years	Encapsulated cyst	Curettage	Typical osteitis fibrosa	
16032	W	M	20	Femur, lower	Fracture, 5 years	Encapsulated cyst			Well 2 years
15398	W	F	2½	Tibia, lower	Tumor 1 year	Healing cyst	Exploration	Typical osteitis fibrosa	Well 8 years
14131	W	M	16	Humerus, shaft	Pain, 1 month	Expansion, fracture	Curettage	Typical osteitis fibrosa	Well 7 years
13831	W	M	16	Tibia, shaft	Trauma, 3 years	Expansion, encapsulated	Exploration	Typical osteitis fibrosa	Well 7 years
13857	W	F	7	Femur upper	Limp, 7 months	Encapsulated cyst	Excision	Typical osteitis fibrosa	Well 8 years
13393	W	F	9	Humerus, shaft	Trauma, 5 days	Cystic, encapsulated	Curettage	Typical osteitis fibrosa	Well 16 years
13259	W	F	8	Humerus, upper	Fracture 10 days	Healing cyst	Excision	Typical osteitis fibrosa	Well 16 years
12731	W	M	6	Humerus, upper	Fracture	Cystic, encapsulated	Curettage	Typical osteitis fibrosa	Well 9 years
10824	W	M	5	Femur upper	Tumor	Encapsulated cyst	Curettage	Typical osteitis fibrosa	Well 4 years
10474	N	M	15	Humerus, upper	Pain, 3 weeks	Encapsulated cyst	Curettage	Typical osteitis fibrosa	Well 10 years
10278	W	F	3½	Humerus, upper	Trauma, 2 years	Fracture through cyst	Curettage	Typical osteitis fibrosa	Well 12 years
9732	W	M	13	Humerus	Fracture	Encapsulated cyst	Curettage	Typical osteitis fibrosa	Well 13 years
9718	W	F	40	Fibula, lower	Tumor 25 years	Encapsulated cyst	Curettage	Typical osteitis fibrosa	Well 3 years
9460	W	F	21	Femur lower	Trauma, 6 months	Encapsulated cyst	Amputation	Typical osteitis fibrosa	Well 10 years
9134	W	M	12	Humerus	Tumor 3 years	Encapsulated cyst	Curettage	Typical osteitis fibrosa	Well 2 years
9023	W	F	6	Ulna	Tumor 7 months	Cystic, expansion			Well 16 years
8314	W	F	21	Femur lower	Tumor 10 years	No[t] not[ed]	Amputation	Typical osteitis fibrosa	Well 20 years
6991	W	F	11	Tibia, upper	Tumor 1 year	Cystic, expansion	Curettage	Typical osteitis fibrosa	
6533	N	F	39	Femur lower	Tumor 5 years	No note	Resection	Typical osteitis fibrosa	Died of hemorrhage
6379	W	F	7	Femur upper	Trauma, 4 months	Cystic, expansion	Resection	Typical osteitis fibrosa	Well 20 years
4973	W	M	8	Humerus, upper	Fracture	Cystic, expansion			
3093	W	F	7	Humerus, upper	Fracture, 1 year	Cystic, expansion	Incision	Typical osteitis fibrosa	Well 17 years

* "Upper" and "lower" indicate metaphyseal regions.
† In this and other tables the symptom given is the symptom at time of onset.

lesion, such as parathyroid tumor precocious puberty or skin pigmentation is present. In the first three forms, the calcium and phosphorus values in the blood serum are within normal limits in the last variety blood-chemistry studies may show hypercalcemia and a lowered phosphorus content. This last group includes both hyperparathyroidism and so-called fibrous dysplasia of bone

ROENTGENOLOGIC DIAGNOSIS

The roentgen examination of the typical *solitary bone cyst* (Fig 179) *reveals an* ununited epiphysis near the lesion, indicating youth, central bone destruction in a metaphyseal location, and a fusiform expansion *of thin cortical bone about the defect* Across the cyst, trabeculae extend in irregular fashion, and when pathologic fracture occurs, the margins of the fracture show by their increased density an attempt at spontaneous healing The cortex about a bone cyst, although thinned, is rarely perforated except at the site of fracture The smooth intact bone shell in this lesion is an important diagnostic sign of its benignity Roughening of the surface with radiating spicules of bone or periosteal lipping is more typical of osteogenic sarcoma. Melting away of the shell at one point without sequestration should also arouse suspicion of the osteolytic form of osteogenic sarcoma— the malignant bone aneurysm" (Fig 158) Rarely a gumma of the bone may simulate a cyst (Fig. 184) but perforation of the expanded cortex, periosteal involvement and sequestration, as well as the Wassermann reaction, should aid in making the diagnosis. Brodie s abscess is a smaller lesion, more painful, usually in the tibia and rarely expands bones. Giant-cell tumor is distinguished by the greater age of the patient, the uniformity with which it involves the epiphysis instead of the metaphysis, and the greater tendency for the cortical bone to be asymmetrically expanded and perforated. Chondromyxomas are most difficult to distinguish from this more benign



Fig. 179 Roentgenogram of a typical *bone cyst. The lesion occupies the shaft* of the upper humerus, just below the unossified epiphyseal line. Note the destruction of the medullary bone, the expansion of the cortex, the trabeculated lines and the pathologic fracture. In 45 per cent of the cases, a pathologic fracture is the first clinical sign of a bone cyst.

lesion (see p 94) The chondromyxoma or chondroma is more frequently found in the small bones of the hands and feet and about the ribs and spine, but produces an

area of bone destruction very similar to a cyst. When occurring as a central lesion in the long bones—an extremely rare finding—the chondroma is more finely multiloculated. Bending deformity in the region of the defect in the bone favors the diagnosis of benign bone cyst, since it indicates a

shell, and further toward the interior is the cavity which most frequently contains a straw-colored fluid.

Bloodgood has ably given a classification of the variations in the gross pathologic changes in these cavities or cysts. They may or may not have a connective-tissue lining,



FIG 180 (No 43640) (A) Roentgenogram of a giant-cell variant of a bone cyst on the shaft side of the epiphyseal line in the lower end of the radius before roentgen therapy (B) roentgenogram of the same lesion in the lower end of the radius, after roentgen therapy (L. T Lewald, Professor of roentgenology New York University New York, N Y)

chronic disturbance, to which the bone has become adjusted. Bending of the bone may also occur with chondromas. Neighboring areas of increased density suggesting a healing reaction, and reossification with filling in of the rarefied zone are typical of fibrous dysplasia (Fig 182)

GROSS PATHOLOGY

At operation the bone overlying the cyst varies in thickness according to the duration of symptoms, the thicker shell in old cysts indicating that a healing reaction is taking place (Fig 186) A connective-tissue lining is usually found beneath the bone

and fluid or solid fibrous tissue may be within. Calcium spicules like snow may be found on the inner side of the lining, or the remains of tissue resembling the giant-cell tumor may be disclosed.

The contents of the cavity when explored give little or no clue to an area of new cartilaginous bone such as the clinical features of age incidence and location would lead one to expect. In the shell of bone overlying the cavity there is frequently an induration extending into the fibrous lining which suggests the formation of new bone, but the location indicates that this is proceeding from the cortical region of the sha

rather than from a central metaphyseal location. Aside from this cortical reaction the gross specimens suggest a process of bone destruction rather than one of bone formation.



FIG. 181 Roentgenogram of a latent bone cyst found accidentally after injury There is a thick shell of cortial bone about the lesion and the cancellous bone at the margin of the cyst is increased in density

MICROSCOPIC ANALYSIS

A microscopic analysis of the bone cyst fails to disclose in most instances a bone destructive process which would explain the cavity formation Much of the tissue composing the cyst wall is fairly uniform and consists of spindle cells and fibroblasts, among which there is much clear intercellular substance (Fig 187)

The tissue varies in relation to special areas. These special areas are of three main types (1) cysts with or without old hemorrhage (2) bone islands or bone trabeculae and (3) vessels in areas of fresh hemor

rhage Attention is first directed to the cyst wall About the cyst wall the connective tissue is condensed to form a fibrous lining (Fig 187) Behind this lining embryonic found. In the larger cysts this is less likely to occur

Around the bone spicules, the first or proximal row of cells is an actively prolif



FIG. 182. (No 32732) Roentgenogram of a case of diffuse fibrocystic disease or fibrodysplasia. The entire shaft of the bone is diffusely involved. The bone has bowed anteriorly because of its increased length and weakened condition. Reossification has nearly kept pace with bone destruction.

fibroblasts are laying down intercellular substance, with the formation of osteoblasts and the direct proliferation of new bone. Occasionally giant-cell areas with round cells will be seen. Within the smaller cysts the remains of old hemorrhages are often erating layer of osteoblasts and numerous gradations between these cells and fibroblasts (Fig. 188) Beyond, there is generally a loose fibrous tissue, almost myxomatous in appearance. Apparently the cycle is from spindle cells to fibroblasts to osteoblasts and

then to bone formation, the bone at first being osteoid tissue previous to calcification.

Frequently an area with fresh blood will have a mixture of round and spindle cells proximal to a new vessel and there will be seen a sprinkling of large giant cells of the *epulis* type (Fig. 169) This relation of round cells and giant cells to spaces with red blood cells is most significant. While some feel that giant cells are called on to absorb these hemorrhagic deposits (Konjetzny) the giant cells are associated only with new vessels and fresh hemorrhages rather than with the old blood and represent foci of active angiospongiosa preparatory to mineral substitution. For this reason it is more probable that the order of pathologic events, so far as microscopic analysis can disclose them, is (1) the formation of giant-cell areas followed by the development of new blood vessels and hemorrhage, (2) the absorption of hemorrhage with cyst formation and (3) the lining of the cyst by fibrous tissue which is gradually transformed into bone. In any event the three processes of hemorrhage cyst formation and new bone construction which represent the special areas in osteitis fibrosa seem to be related and to have a definite influence on the character of the lesion.



FIG. 183. (No. 34560) Roentgenograms of bone cysts with spontaneous healing (*Left*) Spontaneous healing of bone cyst following fracture. (*Right*) Spontaneous healing of bone cyst, with progression toward the midshaft region.

Minute areas of calcification are often seen in the new bone laid down in osteitis fibrosa. Bone via cartilage as seen in osteogenic sarcoma, however has not been ob-

Konjetzny G. E. Die sogenannte "lokalisierte Osteitis Fibrosa," Arch. f. klin. Chir 121 567 19__



FIG. 184 (No. 43020) Congenital syphilis of the bone with formation of a gumma suggesting in the roentgenogram a bone cyst or a Ewing's sarcoma. The periosteal reaction and the perforation of the cortex is against the bone cyst and in favor of sarcoma or inflammatory lesion. The Wassermann was 4 plus and the patient was age 7

served, neither has true myxomatous tissue. Although much has been said about myxomatous degeneration in osteitis fibrosa, the interpretation placed on such areas here is that they are loose embryonic connective tissue.*

NATURE OF OSTEITIS FIBROSA

The foregoing analysis of the histology of the cyst wall leads to the conclusion that the pathologic process is one of fibrous proliferation and new bone formation and therefore concerned with repair or healing. We do not see in this tissue evidence of an inflammatory reaction although repair in bone following a medullary abscess may show the same healing phases as osteitis fibrosa.

This view of the nature of osteitis fibrosa or bone cyst is substantiated by the experimental work of Macewen.† He found, as we do in sections taken from numerous areas in the bone, that regeneration takes place independently of the periosteum. The patients suffering from the lesions considered here are in the younger period of life when (as Macewen has pointed out) the proliferating power of the bone cell is at its height. The bone involved by the disease reacts vigorously and we find bone formation taking place through the activity of osteoblasts in a medium of fibrous tissue, without the transitory stage of cartilaginous calcification. Sections of the cyst wall show an exact duplicate of the process depicted in Macewen's book on new bone, produced experimentally growing inside of glass tubes.

The conclusion that osteitis fibrosa represents a healing reaction in bone, indicates that it should not be considered a pathologic entity In accordance with this view are the initial records made during this study Here histologic diagnosis in the absence of other data in the osteitis fibrosa

* This loose embryonic connective tissue, as pointed out by Leriche and Policard (Physiology of Bone St. Louis, Mosby 1928) is a precursory edema pervading the connective tissue, and is always the first step in bone formation in this tissue

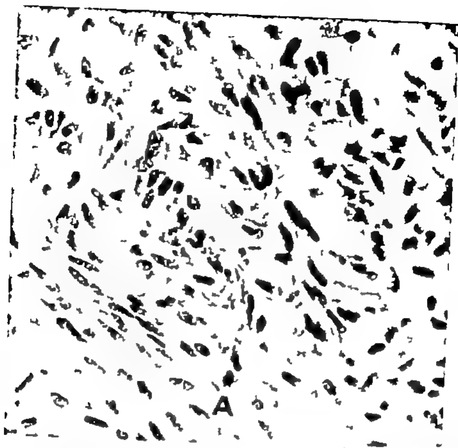
† Macewen, W: The Growth of Bone, Glasgow James Macelhose and Sons, 1912, Figs. 27 and 28

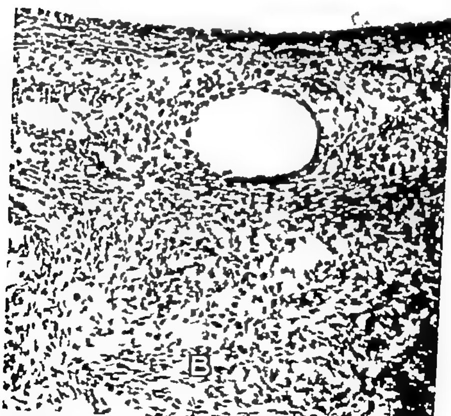


Fig. 185. Roentgenograms of a bone cyst of the the shaft of the radius of a child, aged 6 years. (*Left*) The film depicts the lesion in January 1923 prior to irradiation. (*Center*) The lesion in October 1924 after two courses of irradiation. (*Right*) The healed lesion in August, 1925 18 months after the last treatment. Such irradiation is not advised because of the danger of arresting bone growth.



Fig. 186. (No. 8324) Gross specimen of a large bone cyst of 10½ years duration in the lower end of the femur in a woman, aged 21. There is an unusually large amount of fibrous tissue and new bone formation in the cyst wall because of the age of the lesion.





Fro Nos. 40124 and 24746) Two typical areas of osteitis fibrosa l A the intercellular substance is emphasized. In (B) there is sation of fibrous tissue in the wall of the large cyst. A small lso is shown.

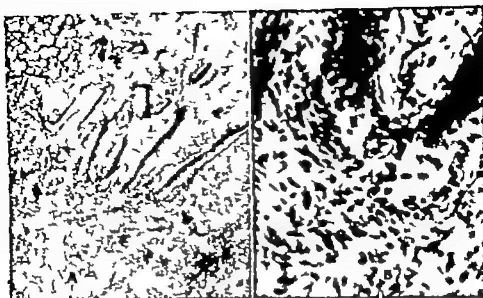


Fig. 168. (No. 19179) (A) low-power and (B) high-power magnification of new bone formation in osteitis fibrosa. Osteoblasts derived from fibroblasts are laying down osteoid tissue These spicules of new bone are characteristic of the process termed fibro-ostosis.



Fig. 169 (No. 28609) Photomicrograph from a bone cyst showing a newly formed cyst containing red blood cells and surrounded by a sprinkling of giant cells.

group showed the largest percentage of error Abscess walls, bits of capsule from central sarcoma of bone, or secondary meta



FIG. 190 (No 36614) Bone cyst formed about a foreign body (A) is a roentgenogram and (B) is a photomicrograph from the same case. The patient was struck by a piece of flying steel 18 months previously the steel entering the hand. The superficial wound healed. Fourteen months later swelling and pain occurred at the site of injury The roentgenogram shows the cyst about the foreign body The photomicrograph shows fibro-ostosis (new bone and fibrous tissue) surrounding an area of granulation tissue.

static tumor cases of fibrous dysplasia and periosteum overlying ossifying hematoma were all inadvertently placed among the sections classed as osteitis fibrosa. From a standpoint of microscopic diagnosis, it was a veritable dumping ground. The reasons for this are to be found in the nonspecific nature of the tissue reaction, erroneously termed osteitis fibrosa. It is not an inflammation in fibrous tissue or in bone but a process of repair constituting a natural defense of cancellous bone, cortical bone endosteum and periosteum against inva

sion whether the invading lesion is an abscess, a sarcoma, or a giant-cell tumor (Figs. 190 and 191)

In most cases of osteitis fibrosa this healing reaction is found around an area of bone destruction. The solitary bone cyst shows progresses without marked symptoms, for when we recognize the condition clinically and explore, the bone-destructive phase is complete and nothing is encountered but the healing phase. This process of repair sometimes extends over 10 or more years



Fig. 191 (No. 15745) Section taken from the margin of a Ewing's sarcoma of bone. The undestroyed bone is reacting to form a protective wall about the tumor laying down new bone surrounded by osteoblasts. These new bone spicules with the surrounding fibrous tissue resemble osteitis fibrosa A nest of round sarcoma cells is seen in the upper portion of the picture

such an area in the form of a cavity and about it is the typical healing reaction which we have termed fibro-ostosis (indicating new bone formed directly from fibroblasts) The reparative nature of this reaction of fibro-ostosis is evidenced clinically by the benign course of the disease and the tendency of the lesions to undergo spontaneous healing. Clinically and pathologically it would seem that the bone-destructive process soon becomes arrested or often and then a latent bone cyst is found. The persistence of the cyst is the result of nature's difficulty in collapsing the walls, and when fracture or a crushing procedure at operation aids in collapsing this cavity the lesion heals.

TREATMENT

This fundamental healing tendency in cases of bone cysts and the function played in the process by collapse of the walls of the

cavity must be borne in mind in treatment. These features of pathologic physiology warrant a most conservative attitude, and argue against operative interference when the symptoms are negligible or when pathologic fracture with impaction offers the possibility of obliterating the cavity with ultimate healing. Crushing of the cyst wall or curettage followed by the implantation of bone chips is the treatment of choice (see end of Chap 11)

SUMMARY

The benign solitary bone cyst is a frequent lesion in children under 15 years. This lesion usually occurs in the shaft near the upper metaphysis of the humerus femur or tibia and runs a protracted and benign course with mild symptoms, averaging 2½ years. Pathologic fracture is usually the only acute phase of the disease and is one of the most frequent reasons for consulting the physician In the roentgenograms this tumor shows a central bone-expanding defect, the contours of which are symmetrical and have a *smooth and intact outline*. The cavity in the bone may be traversed by lines of trabeculation. Pathologic fracture with tendency to healing may occur In the gross and under the microscope the lesion shows a healing reaction of fibrous tissue and new bone formation about the cavity which contains the remains of old hemorrhage or straw-colored fluid.

Arrest of the lesion without obliteration of the cavity results in the latent bone cyst. Progression of the disease when the presence of the cyst is complicated by parathyroid tumor or general skeletal disease is discussed in Chapter 11, which follows. The details of treatment are also given in Chapter 11.

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11

Histologic Variants of the Bone Cyst and the Multiple Form of Osteitis Fibrosa (Von Recklinghausen's Disease)

A study of the variant forms of the bone cyst discloses the nature of the bone-destructive process responsible for these lesions. These variant forms of bone cysts include acute cysts with the duration of symptoms under 6 months (compared to the average duration of 2½ years for typical cysts) polycystic lesions and progressive multiple osteitis fibrosa, so-called von Recklinghausen s disease (Tables 26 27 and 28) Histologic examination of tissue removed from these conditions usually discloses microscopic features characteristic of giant cell tumor

Acute or early cases of bone cyst show a metaphyseal location and a polycystic structure. The symptomatology in these cases is brief and clinically and pathologically these lesions are often confused with giant-cell tumor (Fig. 192) Twenty nine in the series of 275 cases of bone cysts were in this group Microscopically they were all classed as giant-cell variants. By this is meant that large, multinucleated giant cells embedded in hemorrhagic stroma, typical of a giant-cell tumor were always found in early cases of bone cysts examined pathologically This confirms the microscopic analysis of the typical bone cyst, presented in the foregoing chapter where on histologic grounds it was assumed that the giant-cell areas preceded those of fibro-ostosis.

In other words, the bone-destructive phase of osteitis fibrosa is characterized by tissue typical of a giant-cell tumor More broadly stated, the average solitary bone cyst in the long bones is a healed or healing giant-cell tumor Twenty-nine early cases of 275 cases of bone cyst show marked giant-cell areas, and 60 cases of giant-cell tumor of a series of 300 cases show a healing change toward osteitis fibrosa, most marked at the margins of the tumor but also infiltrating toward the center

This does not mean that all bone cysts are healed giant-cell tumors, nor that giant cell tumors will all progress toward a healed state of osteitis fibrosa. In bone cysts 2 per cent of the cases can be shown to have a bone-destructive phase due to a foreign body (Fig 190) or an abscess, and in about 20 per cent of the cases rather loosely classed as osteitis fibrosa some primary disease such as osteomalacia, Paget s osteitis deformans, fragilitas ossium, or fibrous dysplasia is responsible for this cyst formation. The majority of solitary bone cysts (78 per cent) however show their relationship to a preceding giant-cell-tumor phase (1) by the persistence of giant-cell areas most frequent in the younger cysts with a shorter

duration of symptoms, and (2) by the fact that these lesions are on the metaphyseal side of the epiphyseal line, bordering on the epiphysis in which giant-cell tumors occur

The *polycystic* group of osteitis fibrosa also emphasizes the relation of the bone cyst to giant-cell tumor tissue, for in these lesions the small young cysts are found to

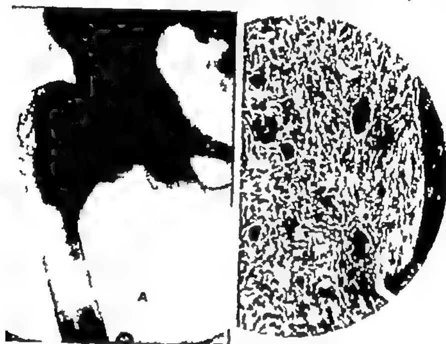


FIG. 192. (No. 17121) Giant-cell variant of osteitis fibrosa near an epiphysis. The roentgenogram, (A) shows a lesion in the region of the greater trochanter which is inclined to be polycystic. There has been a pathologic fracture The photomicrograph, (B) from the same case shows numerous giant cells embedded in the stroma of fibro-ostosis.

arise in giant-cell areas, fusing together to form the larger cavities.

In cases of multiple cysts in von Recklinghausen's disease associated with parathyroid adenoma, both giant-cell tumors and typical cysts may be found in the same patient, emphasizing the fact that the two lesions are different phases of the same process.

ACUTE BONE CYSTS OR GIANT-CELL VARIANTS OF THE BONE CYST IN THE METAPHYSEAL ENDS OF THE LONG BONES

Clinically these lesions are of shorter duration than the typical bone cyst. The average duration in the group of cases in Table 26, 27 (with two exceptions) is six months. None of these lesions is found in the region of the midshaft. Their location is invariably on the shaft side of the epiphyseal line close to the area in which typical giant-cell tumors occur A favorite site for these hybrid bone cysts is the region of the greater trochanter in the femur (Fig. 192) Here, it will be recalled, there is a separate epiphyseal line in young patients, indicating that the transformation of cartilage to bone taking place in this locality has some bearing on the pathologic process.

In the roentgenogram and in the gross this group of lesions is inclined to be more subcortical than central in location, and the structure is most frequently trabeculated. When this polycystic character was particularly marked under the microscope, the lesions were grouped under the classification of polycystic osteitis fibrosa.

On microscopic examination the present group of cysts contain giant cells which are

smaller have fewer nuclei and are more sparsely distributed than in a typical giant cell tumor located in an epiphysis. In the stroma, too, there are more fibroblasts, more intercellular substance and more bone islands. However small areas of larger giant cells surrounded by a narrow zone of endothelial cells are met with here tumor and should be treated more radically than the former and more conservatively than the latter They often respond favorably to irradiation, as is pointed out below

POLYCYSTIC OSTEITIS FIBROSA

Two views may be taken concerning these lesions, which are generally referred to by



FIG. 193. (No. 34990) A giant-cell variant of osteitis fibrosa in the metaphysis (roentgenogram and section from the same case) (A) the lateral and anterior roentgenogram views, showing the typical fusiform lesion of the bone cyst extending to the epiphyseal line. The duration of symptoms was four months. (B) is a photomicrograph of one of the numerous giant-cell areas found amid the osteitis fibrosa tissue in this lesion, demonstrating the tendency of the bone cyst to assume a giant-cell structure when it borders on the epiphyseal line in an early stage of the disease.

and there in the sections (Fig. 193) Hemorrhages are a rather prominent feature, and here the giant cells dispose themselves about the hemorrhage and about the cyst wall. The bone spicules are the same as those found in typical cysts and are surrounded by osteoblasts.

This histologic picture is related to the brief duration of the symptoms and to the proximity of the lesion to an epiphysis. The brief course site and histology are important in singling out this type of cyst for individual treatment. They stand midway between the typical bone cyst and giant-cell the name of polycystic osteitis fibrosa. One view is that they are an early stage of bone cyst, assuming a structure characterized by an aggregation of small cysts because a fusion of these small cavities at a later date represents the mode of origin of the large solitary cysts. The second view is that such lesions are a more progressive form of bone cysts, and that their continued growth by the apparent budding of small cavities represents a transition between the solitary bone cyst (which is an arrested lesion) and the multiple form of osteitis fibrosa, which is undoubtedly pro-

gressive. Some truth resides in both these views.

A survey of the cases in our series and those from the literature shows that in many cases the multiple bone cysts take on the structure of polycystic lesions. Hence, the peculiar multilocular structure is associated with the progressive nature of generalized osteitis fibrosa. On the other hand, when this polycystic structure is observed in a single bone (Fig. 194) these lesions occur near the epiphyseal line, in the metaphysis, indicating an early stage in the transition from giant-cell tumor to an arrested cyst. Under the microscope these small cysts are surrounded by tissue rich



FIG 194 (No 28609) (A) polycystic osteitis fibrosa invading the epiphysis of the fibula (B) photomicrograph showing beginning of fusion in several small cavities. Note the association of red blood cells with the cysts.

TABLE 26. VARIANTS OF OSTEITIS FIBROSA IN THE METAPHYSEAL ENDS OF LONG BONES

Path. N	Race	Sex	Age	Location	Symptoms	Roentgen Findings	Treatment	Microscopic Appearance	Results of Treatment
40236	W	M	10	Femur lower	Trauma, 20 months	Shell perforated	Curettage	Giant-cell areas in osteitis fibrosa	Well 20 yr
35508	W	M	15	Femur condyles			Curettage	Giant-cell areas in osteitis fibrosa	Lost
35253	W	F	5	Tibia, upper	Trauma, 10 weeks	Cystic, expansion	Curettage	Giant-cell areas in osteitis fibrosa	Discharged, well
34400	W	F	7	Tibia, upper	Trauma 4 months	Cystic, expansion	Curettage	Giant-cell areas in osteitis fibrosa	Well 1 year
34176	W	F	14	Femur trochanter	Pain 1 year	Cystic, expansion	Curettage	Giant-cell areas in osteitis fibrosa	Well 5 years
33882	W	M	6	Femur trochanter	Pain, 4 months	Cystic expansion	Curettage	Giant-cell areas in osteitis fibrosa	Well 3 years
32392	W	F	27	Femur trochanter	Trauma, 13 years	Polycystic, expansion	Curettage	Giant-cell areas in osteitis fibrosa	Well 3 years
32013	W	M	12	Femur lower	Pain 3 months	Cystic, expansion	Curettage	Giant-cell areas in osteitis fibrosa	Well 5 years
19179	W	F	31	Femur lower	Trauma, 5 months	Cystic, fracture	Amputation	Giant-cell areas in osteitis fibrosa	Well 12 years
18371	W	F	23	Femur trochanter	Pain 6 years	Cystic, fracture	Curettage	Giant-cell areas in osteitis fibrosa	Well 11 years
17121	W	M	18	Femur trochanter	Fracture	Polycystic, expansion	Curettage	Giant-cell areas in osteitis fibrosa	Well 9 years
16207	W	F	13	Tibia, upper	Trauma, 7 months	Cystic, expansion	Curettage	Giant-cell areas in osteitis fibrosa	Well 14 years
15893	W	M	5	Femur upper	Trauma, 7 months	Cystic, fracture	Curettage	Giant-cell areas in osteitis fibrosa	Well 5 years
10093	W	F	19	Fibula, lower	Tumor 11 months	Cystic, expansion	Resection	Giant-cell areas in osteitis fibrosa	Well 15 years
10332	W	M	12	Humerus, upper	Trauma, 2 years	Cystic, fracture	Curettage	Giant-cell areas in osteitis fibrosa	Well 5 years
5644	W	M	18	Humerus, lower	Pain [illegible] months	Shell perforated	Excision	Giant-cell areas in osteitis fibrosa	Well 24 years

Lesions similar to those in this table but with marked polycystic structure are shown in Table 27

TABLE 27 POLYCYSTIC LESIONS

Path No	Race	Sex	Age	Location	Symptoms	Treatment	Roentgen Findings	Microscopic Appearance	Results of Treatment
Metaphyseal Location									
37003	W	F	19	Humerus, upper end	Trauma, 2½ months	Exploration	Polycystic	Giant cell areas in osteitis fibrosa	Well 3 years
22324	W	F	22	Tibia, malleolus	Trauma, 6 months	Curettage	Polycystic	Hemorrhage cysts with giant cell areas	Well 3 months
28608	W	F	12	Fibula, upper end	Trauma, 6 weeks	Resection	Polycystic	Small cysts surrounded by giant cell areas	Well 5 years
30043	W	F	22	Finger phalanx	Tumor 6 months	Amputation	Polycystic	Hemorrhage cysts surrounded by giant cell areas	Well more than 1 year
13214	W	M	42	Femur lower end	Tumor 6 months	Resection	Polycystic	Multiple cysts with giant cells	Well 5 years
12507	W	F	5	Tibia, upper end	Fracture, 16 months	Curettage	Polycystic	Small cysts surrounded by giant cell areas	Well 26 years
11486	W	M	29	Tibia, malleolus	Tumor 4 years	Curettage	Polycystic	Hemorrhagic cysts surrounded by giant cell areas, fibrous stroma	Discharged, well
5898	W	M	22	Femur trochanter	Fracture, 3 months	Curettage	Polycystic	Cysts surrounded by giant cell areas	Well 16 years
Multiple Bone Involvement									
62120	W	F	14	Tibia, humerus, pelvis	Pain bending deformity 2 y		Multiple cysts		
62046	W	F	35	Tibia, ulna, hands	Tumor fracture				
61225	W	M	16	Temporal bone, tibia, clavicle spine	Tumor bending deformity 3 years				
56462	W	M	20	Humerus, femur pelvis	Pain, tumor 1 year				Well 8 years
54260	W	F	44	Mandible, ribs, pelvis	Pain fracture 1 month				Well 10 y
53798	W	F	9	Ribs, pelvis, femur				Removal parathyroid adenoma	
51096	W	M	25	Pelvis, humerus, femur	Pain, fracture 2 years				Dead, nephritis 3 years later
48502	W	M	15	Multiple bones	Trauma, pain, 5 years Tumor fracture 12 years				Dead 3 yr
									Lost
37250	W	F	21	Humerus, tibia, radius	Tumor 3 years	Exploration	Polycystic	Small cysts surrounded by giant cell areas	Well 3 years
33358	W	F	34	Humerus, tibia	Trauma, 2 years	Curettage	Polycystic	Small cysts surrounded by giant cell and spindle cell areas	Unimproved
32733	W	F	5	Tibia	Tumor 3 years	Exploration	Polycystic	Cysts surrounded by giant cell areas	Well 15 yr
30634	N	M	12	Tibia, fibula, foot	Trauma, 6 months	Curettage	Polycystic	Hemorrhage cysts ... giant cell areas	Discharged, well

in large multinucleated giant cells (Fig 195) This microscopic structure shows that elements of the bone-destructive process persist and that the arrested stage characterized by fibro-ostosis and a scarcity of giant cells has not yet been reached. This lack of complete healing is explained either by the short duration of the symptoms and the proximity of the lesions to the epiphyseal line or by the presence of multiple bone involvement indicating a generalized disease of the skeleton (Table 27)

Knaggs, in a review of osteitis fibrosa, stated that he was convinced that there is an earlier bone-destroying stage in bone cysts but remarked that he had never seen such an early stage This early stage is seen in all giant-cell variants of osteitis fibrosa, and nowhere is it better exemplified than in polycystic lesions. The duration of symptoms in this group of lesions averages about five months compared to two and a half years for typical bone cysts. In the roentgenogram, these lesions are found most often in a subcortical location rather than centrally and this asymmetrical position is characteristic of both early giant-cell tumors and early bone cysts. Histologically the multiple small cysts filled by blood and surrounded by giant cells indicate a transitional form between the giant-cell tumor and the bone cyst. Their clinical behavior resembles that of giant-cell tumors. The origin of bone cysts from giant-cell tumors has been conclusively demonstrated in cases of giant-cell tumor treated by irradiation. The arrest of the giant-cell tumor by adequate irradiation may result in the formation of a typical bone cyst (Fig. 196)

MULTIPLE CYSTS AND SO-CALLED MULTIPLE GIANT-CELL TUMOR (VON RECKLINGHAUSEN'S DISEASE)

Contributions to this subject show that a clinical and pathologic overlap has long been recognized in this group of multiple tumors.* Morton,† in reviewing the literature of multiple bone cysts, divides the lesions into "group 1 without giant-cell sarcoma and group 2 with giant-cell sarcoma." In a similar manner Alexander and Crawford‡ divide multiple giant-cell tumors into two groups, those without and those with associated fibro-cystic osteitis.

The explanation of the histologic overlap between cyst and giant-cell tumor in these diffuse lesions of the skeleton can be explained by the progressive and hence recent state of the pathologic changes. The reason for the multiplicity of the tumors is more widely recognized and has been well established. After von Recklinghausen,§ in 1891, separated his entity of multiple bone cysts, Askanazy|| (1901) and later Erdheim¶ (1907) called attention to the general metabolic disturbance of the bones associated with pathology in the parathyroid glands. Mandl** (1926) conclusvely proved the endocrine basis underlying multiplicity of the tumors by removing a parathyroid tumor and obtaining clinical improvement in a case of multiple osteitis fibrosa. Since this date many contributions (Hunter †† Ballin and Morse, etc.‡‡) have emphasized the endocrinology of this disease.

Thus while local pathologic changes pre-

Knaggs, R. L.: The inflammatory and toxic diseases of bone, New York, Wood, 1926.

* Both Henderson (Minn. Med. 11 542, 1928) and Meyerding (J.A.M.A. 83 1323 (Oct. 25 1924) recognized a relationship between these two tumors in their reports on solitary giant-cell tumors.

† Morton, J J.. The generalized type of osteitis fibrosa cystica, Arch. Surg. 4 433, 1922.

‡ Alexander E. G., and Crawford, W H: Multiple giant-cell tumors, Ann. Surg. [illegible] 863, 1927

§ Von Recklinghausen, F: Die fibröse oder deformirende Ostitis, die Osteomalacie u. Fortschr f. Virchow Berlin, 1891

|| Askanazy M.: Arbeiten a. d. Geb d. path. Anat. u. Bakt. 4 398 1904.

¶ Erdheim, J Sitzungsber d. Akad. d. Wiss., Wien, 3 Ab., 44 811, 1907

** Mandl. F Zentralbl. f. Chir 53 260, 1926.

†† Hunter D: calcium and phosphorus metabolism, Lancet, 1 897 947 999 1930.

‡‡ Ballin, M., and Morse P F: Parathyroidism. Am. J Surg., [illegible] 403, 1931

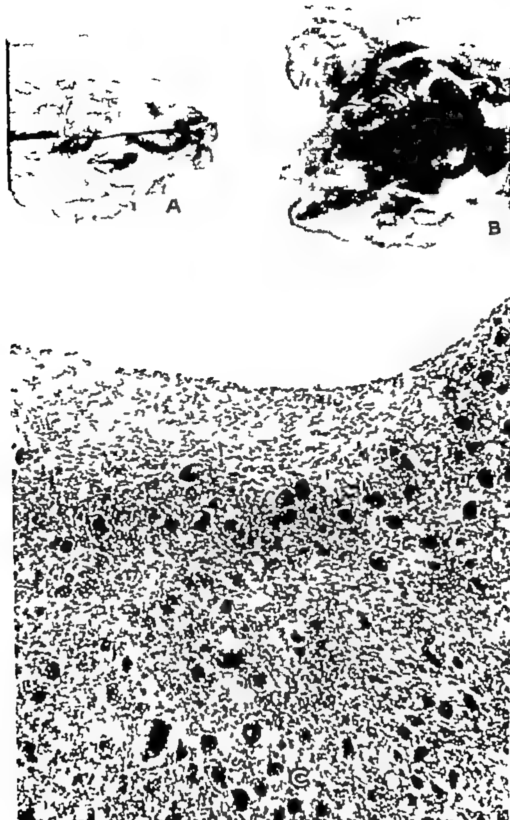


Fig. 195 (No 37250) Multiple giant-cell tumors occurring in the tibia, radius, antrum and both humeri associated with parathyroid adenoma (gross and microscopic specimens from the same case) (A) and (B) are gross specimens showing the polycystic structure of the tumor C is a photomicrograph showing the numerous large multinucleated giant cells occurring in a cyst wall.

dominate in the solitary bone cyst in a patient with a normal blood calcium, a general systemic factor parathyroidism, with elevation of blood calcium, underlies the diffuse invasive character of generalized osteitis fibrosa. In the active state of the disease the lesions have been termed multiple giant cell tumors, in the chronic state multiple bone cysts.

Many important features of diffuse cystic disease are illustrated in the following case (No 37250 Fig 195) The patient, observed in 1922, was a white woman, aged 21, and the condition was of nine years duration. The lesions were in the right tibia, the left radius and both humeri, all occurring just on the shaft side of the epiphyseal line. In addition to this, there was a tumor in the left antrum. The specimens illustrated were from the right tibia. In the gross the tumor was polycystic, and under the microscope small cystic areas were present in large numbers. Giant cells predominated in the tissue about the cyst wall, and among these giant cells were numerous round cells. Elsewhere the stroma was composed of spindle cells and fibroblasts with islands of new bone and typical osteitis fibrosa. There was much hemorrhage in the tissue, and some small cysts were filled with blood.

There were too many giant cells in the sections for simple cysts. Yet, the tumors in the long bones were all on the shaft side of the epiphysis, and the patient was only 15 years of age when these lesions first appeared. These two facts and the polycystic nature of the tumor favor a diagnosis of Von Recklinghausen's disease.

Usually the single bone cyst is an arrested lesion as we have seen, an arrested giant-cell tumor When it is multiple, or particularly when it is polycystic, we have reason to believe that the lesion has become progressive. In the above case the age of onset and the location of the tumors in the metaphyses of the long bones would seem to indicate that had this lesion become arrested, it would have been a typical bone cyst Instead, it progressed, showed multiple bone involvement polycystic structure and a predominance of giant cells. The explanation for this failure to be arrested was an adenoma of the parathyroids that prevented the usual protective overgrowth of fibro-ostosis from taking place

In the first study of this case we had at our disposal only the history the roentgenograms and the microscopic material. The patient was later admitted elsewhere for restudy and hyperparathyroidism with increased calcium excretion, elevation of the serum calcium and lowering of the serum phosphorus was found. At surgical exploration an adenoma of the parathyroid was removed. Exploration of a cystic area in the tibia showed an arrested bone cyst with areas of osteitis fibrosa. Giant-cell areas seen at the first operation had disappeared.

Recent studies leave little doubt that in so-called multiple osteitis fibrosa in which the cystic areas are associated microscopically with giant cells, the underlying systemic disease affecting the skeleton is hyperparathyroidism. Parathyroid adenomas have been demonstrated in an increasing number of cases showing multiple bone

We have studied a similar case the material of which was placed at our disposal through the courtesy of Dr R. M. Wilder of the Mayo Clinic. The patient, a white woman, aged 32, studied by him over a period of four years (reported in Endocrinology 13 231, 1929) had abnormal calcium and phosphorus values in the blood serum which ultimately proved dependent on a hyperparathyroidism associated with a benign adenomatous tumor of the parathyroid gland. Giant-cell tumors occurred in the lower part of the femur the upper jaw and at the site of the right lower bicuspid (epulis) The serum calcium was elevated to 11 4 mg per hundred cubic centimeters and the phosphorus lowered to 1 4 mg. per hundred cubic centimeters. As a result of this removal of lime salts from the bones the pelvis showed rarefaction and distortion similar to osteomalacia and the skull and spine areas of absorption. Improvement followed removal of the parathyroid tumor a diet high in vitamins and ultraviolet light therapy The serum calcium returned to 8.3 mg per hundred cubic centimeters and the phosphorus to 1.8 mg. per hundred cubic centimeters.

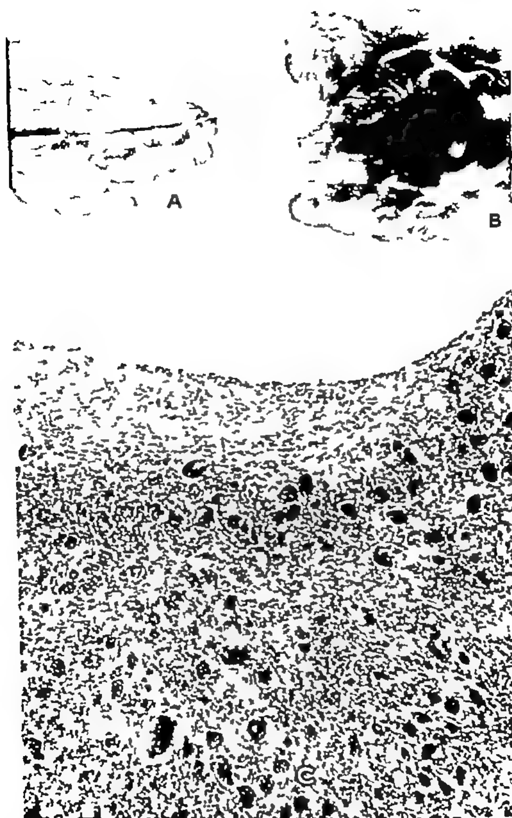


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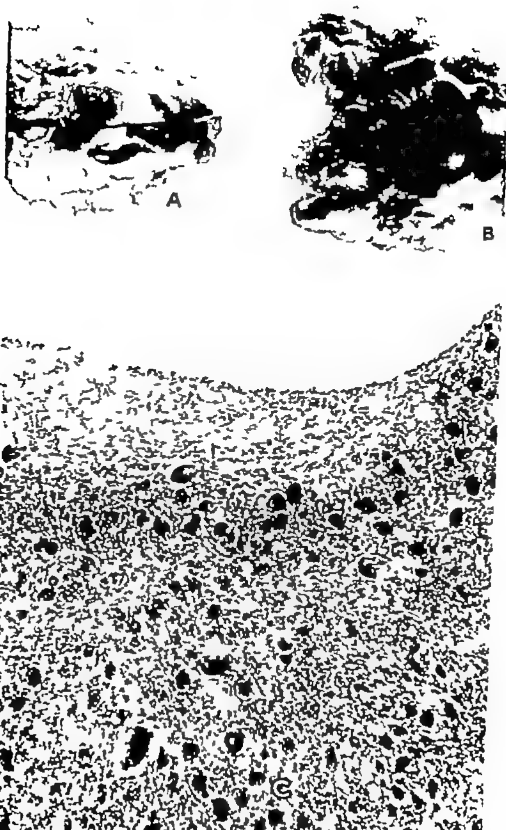


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TABLE 28. MULTIPLE GIANT CELL TUMOR AND BONE CYST

Path No	Race	Sex	Age	Location	Symptoms	Roentgen Findings	Treatment	Microscopic Appearance	Associated Disease	Results of Treatment
37245	W	M	12	Upper humerus, lower radius, upper fibula, femur	Trauma	Cystic expansion	No operation	No note	Osteogenesis imperfecta	Well less than 5 years
36592	W	F	4	Fibula, tibia, os calcis	Deformity 3½ years	Cyst, fracture, bending	Excision	No note	Osteogenesis imperfecta	Deformity still persists
36208	W	M	3	Skull, femora, sacrum	Marasmus	Areas of absorption	Exploration	No note	Rickets	Unimproved
33702	W	F	16	Humerus, radius	Dysfunction 10 months	Cystic perforation	Curettage	Cysts with areas of giant cells	Not determined	Well less than 5 years
37230	W	F	21	Humeri, radius, tibia, upper jaw	Tumor 3 years	No note	Curettage	Cysts with areas of osteitis fibrosa and giant cells	Hyperparathyroidism	Well 3 years
33473	W	F	22	Vertebra, pelvis, femur tibia	Trauma 6 months	No note	Curettage	Cysts with areas of osteitis fibrosa and giant cells	Hyperparathyroidism	Discharged improved
33148	W	M	34	Tibia humerus, radius	Trauma 3 years	No note	Curettage	Cysts with areas of osteitis fibrosa and giant cells	Hyperparathyroidism	Unimproved 3 years later
33181	W	M	18	Fibula, tibia	Trauma 1 month	Cyst with fracture	No note	No note	Not determined	Discharged well
32732	W	F	3	Tibia, multiple	No note	Cystic bending	Exploration	Cysts with areas of giant cells	Rickets	Discharged improved
31580	W	F	25	Fibula, tibia, femur	Fracture 3½ years	Cystic with fracture	No note	Cysts with areas of osteitis fibrosa	Osteogenesis imperfecta	Discharged improved
30316	W	F	32	Scapula, sternum, humerus	Trauma 2 years	No note	No operation, [illegible]	No note	Not determined	Well 7 years
29846	W	F	14	Radius, ulna, femur tibia, fibula	Deformity 7 years	Cystic with rarefaction	No note	No note	Rickets	Discharged improved
29616	W	F	22	J[illegible], pelvis	Tumor 7 months	No note	Curettage	Cysts with areas of osteitis fibrosa and giant cells	Syphilis, congenital	Discharged improved
28074	W	F	18	Femora, tibia	Deformity 12 years	Cystic bending	Curettage	Cysts with areas of giant cells	Osteogenesis imperfecta	Discharged improved
26786	W	F	45	Humerus, ilium, ribs	Fracture 3 years	Shaft of humerus destroyed	No note	No note	No note	Well 7 years
25683	W	F	14	Tibia, ilium, femur	Fracture	No note	Resection	Cysts with areas of osteitis fibrosa and giant cells	Hyperparathyroidism	Died of other causes
23891	W	F	33	Tibia, patella, radius, ulna, humerus	Tumor 6 months	No note	Curettage	No note	Multiple periostitis	Discharged improved
22980	W	F	55	Humerus, tibia	Pain	Cystic bending of spine	Excision	No note	Hyperparathyroidism	Discharged improved
21347	W	F	18	Femur multiple	Pain and deformity 6 years	Bending, rarefaction	Osteotomy	Areas of osteitis fibrosa	Fragilitas ossium	Recurrence
10323	W	F	21	Radius, humerus	Pain 3 years	Cystic, encapsulated	Curettage	No note	Undetermined	Well 20 years

changes typical of the von Recklinghausen type, and in two of the cases in this series a restudy of the patients proved the presence of hyperparathyroidism This also was proved upon restudy in one of the cases reported by Alexander and Crawford. At the present time the data on twelve cases syphilis are accompanied by cyst formation, and adult osseous changes in which cysts are associated with Paget s osteitis deformans, osteomalacia and fibrous dysplasia. Histologically cases in the von Recklinghausen group show spicules of newly formed fibrous bone with active osteoblasts

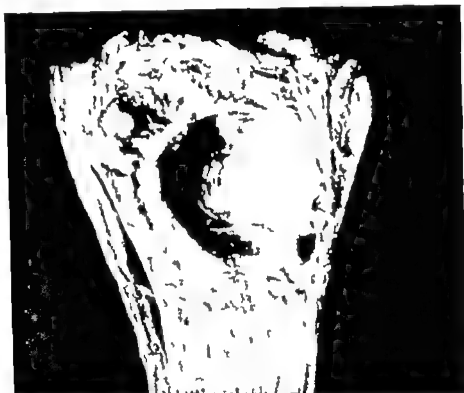


FIG. 196 (No 39134) Gross specimen of a healed giant-cell tumor presenting the pathologic aspects of a typical bone cyst. The original giant-cell tumor was treated by a curettement in October 1925 The section showed organized hemorrhage and areas of typical giant-cell tumor The patient was subsequently treated by irradiation. The leg was amputated in January 1933 because of the changes in the skin overlying the tumor and fixation with pain in the joint.

with multiple osteitis fibrosa and associated parathyroid, adenoma have been studied. The conception of von Recklinghausen s disease is now limited to those cases in which hyperparathyroidism, increased calcium excretion, and a lowering of the serum phosphorus with or without elevation of serum calcium are present, in addition to the skeletal changes. This excludes cases in which juvenile diseases such as fragilitas ossium, rickets and congenital and simultaneous bone resorption by giant cell osteoclasts. The mobilization and excretion of calcium deplete the bone spicules and apparently resorption by giant cells completes the process.

Von Recklinghausen s disease may occur at any age from childhood to late adult life. Depletion of the mineral substances in the skeleton results in a general rarefaction of the bones with bending deformities, spontaneous fractures and definite tumors.

Collapse of the vertebrae may lead to paraplegia. Loss of muscle tone together with the skeletal disturbances, causes these patients to become bedridden. The urinary function is disturbed, polyuria with six to eight times the amount of excretion of calcium occurring in advanced cases. Urinary calculi develop leading to renal colic and hematuria

Colby has discussed this phase of the disease. In thirteen cases in the Massachusetts General Hospital with parathyroid tumors, eight had demonstrable calcification in the urinary tract Three of these cases had bilateral renal stones. Renal colic rather than bone disturbances may be the chief complaint of these patients. Colby found that in some patients parathyroid tumor may result in kidney stones long before demonstrable changes are found in the skeleton. Albright has described cases with renal necrosis caused by diffuse calcific deposits.

Bone involvement is most pronounced in the pelvis, spine and long bones. The skull may be misshapen or show thickening. Occasionally the small bones of the hands or feet are affected (Fig. 197) The outstanding feature is the decreased density of the bones accompanied by one or more definite cysts or giant-cell tumors. The development of giant-cell tumors of the alveolar border (epulis) may be one of the initial symptoms of the disease. Such tumors were present in three of 12 cases in our series. The bone changes are accompanied by symptoms of pain and tenderness. Hyperplasia or adenoma of the parathyroid glands is rarely demonstrable on clinical examination and requires careful dissection of the neck.



FIG. 197 (No. 46918) Multiple cysts and rarefaction of the skeleton with bending deformities associated with hyperparathyroidism. (A) shows cystic condition and bending deformities in the right pelvis and right femur (B) shows diffuse rarefaction, widening and bending in the right fibula.

Estimations of the serum calcium are usually high (roughly between 12 and 20 mg. per 100 cc., as compared with the normal 9 to 11 mg.) Plasma phosphorus is low (1 0 to about 2.0 mg normal 2.5 to 3.5) and plasma alkaline phosphatase is some-

times over 21 Bodansky units, normal 1 to 4 units per cc. The excretion of calcium in the urine may be increased on ordinary diet up to six or eight times the normal (normal 0 3 g in the 24 hours)

In the differential diagnosis of von Recklinghausen s disease metastatic carcinoma, multiple myeloma, and fibrous dysplasia must be considered. In metastatic carcinoma the blood and urinary calcium are not disturbed as a rule, but calcium levels may be elevated following irradiation. Signs of new bone formation are usually visible with carcinomatosis of the skeleton and the primary tumor can often be located. In multiple myeloma Bence Jones bodies in the urine may be demonstrated, and the plasma proteins are elevated. Bone marrow studies following sternal puncture are diagnostic. These changes have never been found in cases of multiple fibrocystic disease. Bending and distortion of the skeleton are less apt to occur in multiple myeloma and metastatic carcinoma. Involvement of the alveolar border in the jaws is seen more often in von Recklinghausen s disease Cystic disease also runs a more protracted course than multiple myeloma, or metastatic carcinoma. In obscure cases the amount of parathormone in the blood can be estimated according to the test of Hamilton. In this test the blood of patients is injected directly into rabbits, and the blood calcium changes in the animal are determined at hourly intervals. Biopsy of the bone may be resorted to in making the differential diagnosis.

Treatment should be directed to the underlying cause of the condition. The parathyroid glands should be explored or irradiated, the patients being put on a diet rich in calcium and phosphorus and vitamin D Merritt and more recently Cutler and Owen have reported an improvement in the osseous condition following irradiation of the parathyroid glands. To date about 200 cases have been reported in the literature in which surgical removal of the hyperplastic parathyroids or parathyroid adenoma has been successfully accomplished (Fig. 199) In some of these cases the condition has recurred in spite of temporary improvement following parathyroidectomy



FIG. 198. A case of Paget s disease of the tibia, with cyst formation. Paget s osteitis deformans is a benign osteitis accompanied by destruction and coarse new bone formation. A widened irregular and mottled zone of cortical bone is typical of this disease. Beneath this cortex, cystic areas of bone resorption are not uncommon.

LATENT BONE CYSTS

The latent bone cyst usually occurs in patients over 30 and may be accidentally

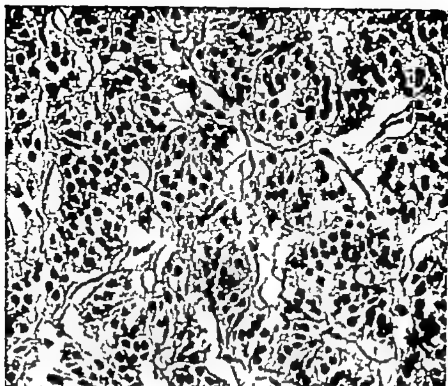




Fig. 199 (Nos. 45438 48959) Photomicrographs of parathyroid adenomas removed from a patient suffering with multiple bone cysts or von Recklinghausen's disease. (A) typical thyroid adenoma, (B) atypical adenoma, showing, on the left, clear cells and, on the right, large syncytial cells.

discovered incident to a roentgen examina tion made for other reasons or the case comes under observation because of mild symptoms, dating over a period of from 5 to 30 years. *Occasionally the patient is in* the second decade and has noted some type of deformity or recalls an injury in the region of the cyst ten or more years previous ly Many of these cases must escape clin ical recognition, for since the advent of frequent roentgenologic examinations, the incidence of this form of cyst is steadily in creasing, constituting at present from about 7 to 10 per cent of all forms of osteitis fibrosa.

In the roentgenogram the latent bone cyst must be distinguished from the rare chon dromatous lesions of the long bones and from a solitary focus of metastatic carci noma or hypernephroma, from Brodie s abscess and from fibrous dysplasia. In adults there is less expansion of the bone than in typical cysts in patients under 15, the walls of the cyst are thicker and slight bending or distortion of the bone may be present in the region (Fig 181) Lines of reossifica tion about the cyst or traversing it in an irregular manner are often seen. When occurring in patients under 30 the lesion usu ally occupies the midshaft, since in this locality it is more prone to produce symptoms and to come under clinical observa tion. In later years it may be accidentally discovered in any region of the shaft.

This form of chronic cyst is not to be con fused with fibrous dysplasia involving a single bone, which may persist throughout the period of bone growth and produces marked bending distortion and overgrowth of the affected member (see Fig 182) The clinical and pathologic features of fibrous dysplasia are described in the chapter which follows.

PROGNOSIS AND TREATMENT

The prognosis as to life is unqualifiedly good in all forms of bone cysts and osteitis fibrosa. The chances of permanent cure as



FIG. 200 A large Brodie s abscess simulating a latent bone cyst. Pain and tenderness at the site of the lesion were important points in the differential diagnosis. At exploration granulation tissue typical of infection was found.

well as the mode of treatment, however vary with the type of lesion

In the solitary latent bone cyst occurring as an accidental finding in an adult in whom symptoms are absent, no treatment is necessary In the typical solitary type of cyst, occurring in a young patient, in whom pathologic fracture has taken place with impac tion and good position, a satisfactory result may follow simple fixation. Operation is not necessary If there is any tendency how ever for the lesion to progress at the end of several months, an operation should be performed, the cavity curetted and its lining stripped from the cyst wall Oblitera tion of the cavity should then be accomplished by filling with bone chips from nearby or from the wing of the ilium or by crushing

In the acute bone cyst or giant-cell var iant occurring in the metaphysis, roentgen therapy in moderate doses is the treatment of choice (see Fig 180) Care must be taken to safeguard the epiphysis from ir

radiation, or bone growth may be arrested. In case of failure with irradiation operative interference such as recommended for the typical bone cyst should be employed.

In multiple osteitis fibrosa an attempt should be made to rule out the possibility of parathyroid tumor and to determine the nature of the underlying systemic condition Studies of the blood serum calcium and phosphorus values should not be omitted. Since most of these diseases contribute to the development of the cysts through their influence on the calcium-phosphorus metabolism, it is important to provide a diet rich in calcium, phosphorus and vitamin D and to give the patient the benefits of sunlight and ultraviolet light therapy If a parathyroid disturbance is suspected on the basis of the blood chemistry and urine studies, these glands should be explored surgically or treated by irradiation

Cure can be expected in the various forms of solitary bone cysts, but progressive deformity in spite of treatment may result in the multiple varieties. Operations for the correction of such deformities in young patients should be postponed until after bone growth has achieved its full maturity

SUMMARY

Variants of the bone cysts and related forms of osteitis fibrosa include the acute bone cysts or giant-cell variant of osteitis fibrosa which occurs on the shaft side of the epiphyseal line in young patients with a duration of symptoms under six months progressive osteitis fibrosa, which diffusely involves a single bone and pathologically is of the polycystic variety multiple osteitis fibrosa, which diffusely involves the skeleton with cystic changes and is associated with parathyroid tumor and disturbances in the calcium balance and the latent bone cyst, a quiescent lesion which is usually accidentally discovered in adults.

The prognosis for life is good in all forms of bone cysts and osteitis fibrosa. Permanent cures vary with the different types of lesions. The latent bone cyst does well without treatment. The acute bone cyst often responds to proper irradiation but may require curettement and filling of the cavity with bone chips. The typical bone cysts may be treated as a simple fracture, if such an accident has occurred, or curetted and collapsed at operation. Progressive, diffuse and multiple forms of osteitis fibrosa should be carefully studied from a systemic and metabolic viewpoint. Lowering of the serum phosphorus with hypercalcaemia warrants exploration or irradiation of the parathyroid glands. A diet rich in calcium, phosphorus and vitamin D with ultraviolet therapy should be tried.

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12

Fibrous Dysplasia

Among the large accumulation of clinical and pathologic material described in the literature as osteitis fibrosa, a series of entities have been separated. One of these, the solitary bone cyst, has long been recognized as a distinct lesion. It is found in the metaphyseal end of the long bones in children. Multiple involvement of the skeleton, with cyst formation, bending deformity and decalcification associated with hyperparathyroidism, is now separated under the heading of von Recklinghausen's disease. This group of cases is easily distinguished by laboratory determinations of the serum calcium and phosphorus and of the blood alkaline phosphatase. The last group of conditions to be separated from the general category of fibrocystic disease of bone has been the multiple and solitary forms of fibrodysplasia.

In 1937 Albright and his co-workers described a syndrome characterized by osteitis fibrosa disseminata areas of pigmentation and endocrine dysfunction, with precocious puberty in females. Previously in 1922, Weil had described such disturbances of bone growth with precocious puberty and Schmorl in 1932 had described such a case as a juvenile osteitis deformans. These cases of polyostotic fibrous dysplasias of bone were reviewed in 1942 by Lichtenstein and Jaffe who were able to collect a total of 90 cases. Of these only 20—all females—showed evidence of precocious puberty with early skeletal maturation. These authors pointed out that in 15 cases only a single bone was affected and suggested that monostotic involvement was probably a common feature of the disease. This was confirmed by a study of fibrous dysplasia in single bones by Schlumberger who reported 67 cases of fibrous dysplasia involving a single bone.

POLYOSTOTIC FIBROUS DYSPLASIA, ALBRIGHT'S DISEASE

Two forms of fibrous dysplasia of bone are now recognized—the diffuse or polyostotic form and the monostotic form. In the diffuse or multiple form, the disease is a congenital anomaly involving multiple bones on one side of the body. Occasionally there is bilateral disturbance. The patient usually comes under observation in childhood or early adolescence. Females are affected more frequently than males.

On roentgen examination the bones are bowed and rarefied with thinning and expansion of the cortex. Pathologic fractures occur. In severe cases the bone deformities may be crippling.

Albright and his associates have emphasized the extraskeletal features of the disease. These include pigmentation of the skin, which occurs in about 35 per cent of all the cases, and endocrine disfunction in the form of sexual precocity in females, which occurs in about 20 per cent. Hyperthyroidism is occasionally recorded. The endocrine and skin changes are more often present if the skeletal lesions are severe or widespread (Figs. 182, 203).

On gross examination the interior of the bone is replaced by grayish-yellowish fibrous tissue which may show islands of cartilage calcification, ossification or minute cyst formation. Vascular areas are occasionally noted. Microscopically the outstanding

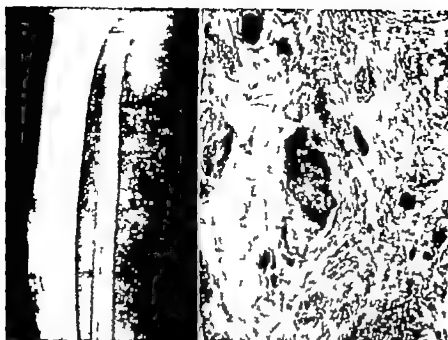


Fig. 201 Fibrous dysplasia in a girl of eight with precocious puberty (*Left*) Roentgenogram showing a bending deformity and cyst formation. (*Right*) Photomicrograph showing fragile and irregular bone trabeculae in a vascular fibrous tissue.



Fig. 202. Roentgenogram and photomicrograph of fibrous dysplasia in a man of thirty

feature is the proliferation of connective tissue which is composed of rather immature spindle cells, either loosely or tightly packed. The spindle-shaped fibroblasts show a tendency to lay down osteoid tissue or bone. Lymphocytes infiltrate the stroma. the primary process is destructive, but areas of increased density may be found. Histologically there is no way of distinguishing some of these lesions from ossifying fibromas of the jaw (Phemister and Grimson).



FIG. 203. Roentgenogram and photomicrograph of polyostotic fibrous dysplasia in an adult.

The osseous lesions may lead to bending of the bone or pathologic fracture.

Polyostotic fibrodysplasia is distinguished from generalized osteitis fibrosa in hyperparathyroidism and renal rickets by its tendency, when multiple, to have a unilateral distribution and by the fact that the lesions are isolated and there is no generalized rarefaction or demineralization of the skeleton. The serum calcium and phosphatase may be moderately elevated during the active stages of disease. However, blood phosphorus is not depressed and there is no increased excretion of calcium in the urine. The disease is often confined to one extremity (monomelic distribution). Its evolution is at first slow and asymptomatic. After an indefinite period, the lesions may become quiescent; they never disappear, however. There is no evidence that localized lesions become generalized; both flat and tubular bones are involved, but the epiphysis is spared. In the roentgenogram

FIBROUS DYSPLASIA OF SINGLE BONES (MONOSTOTIC FIBROUS DYSPLASIA)

The monostotic form of fibrous dysplasia has been reviewed by Schlumberger. The following discussion is based on excerpts from Schlumberger's excellent article through his kind permission. The first sign of the disease is usually a local swelling, particularly if the affected bone is superficial. Local tenderness is sometimes associated with such swelling, and occasionally, when one of the long bones is involved, pain of an arthritic character is referred to the nearest joint. In some of the cases, the disease is not suspected until pathologic fracture occurs.

In contrast to the reported cases of polyostotic fibrous dysplasia, none of the cases show abnormal pigmentation or evidence of endocrine disturbance. The lesion, at time of diagnosis, grows slowly or remains

stationary No congenital abnormalities are found, and the serum calcium, phosphorus and phosphatase are normal.

The distribution of the 67 cases of bone lesions reported by Schlumberger is as follows

Ribs	29
Femur	9
Tibia	8
Maxilla	7
Calvarium	5
Mandible	2
Humerus	2
Ulna	2
Vertebra	1
Pelvis	1
Fibula	1

The small bones of the hands and feet were not affected.

The appearance of monostotic fibrous dysplasia offers, by roentgen examination, little that is characteristic. In the long bones the lesions are found principally in the metaphyses, though occasionally they occupy the middle of the shaft. When the skull is affected, the maxilla is most often involved. Fibrous dysplasia produces an area of radiolucence, sometimes traversed by delicate trabeculae of bone (Fig 202) This zone of rarefaction in the roentgenogram is usually central in position and produces thinning and expansion of the cortex, particularly marked in the ribs and fibula. In Schlumberger's cases, no one thought of fibrous dysplasia when the roentgenograms were read, but, instead, bone cyst, giant cell tumor enchondroma and fibroma were the suspected diagnoses.

The lesions grossly appear as a symmetrically fusiform or almost spherical swelling ranging up to 6 cm. in diameter The surface consists of thin but intact cortical bone. On longitudinal section the cancellous bone and marrow are replaced by a firm, resilient, yellow-white tissue containing occasional small cysts, usually filled with amber fluid. The transition from the pathologic to the normal bone marrow often is abrupt. The abnormal tissue has a gritty character due to the presence of innumerable minute spicules of bone.

Histologically the primary component of the bone lesion is connective tissue, fairly well vascularized and frequently arranged in interlacing bundles and whorls. Within the connective tissue, and most abundant at its periphery are trabeculae of partly calcified, newly formed bone. That this bone is formed by direct metaplasia of the connective tissue is clearly evident from a study of the sections. The sequence of events appears to be as follows The connective-tissue cells round up, the nuclei enlarges and the intercellular fibrils thicken and stain deeply with eosin. Subsequently the intercellular substance increases in amount and ultimately becomes calcified. The incarcerated connective-tissue cells are then indistinguishable from osteocytes. Even the more mature bone trabeculae are deeply penetrated by bundles of collagenous fibers. Not infrequently the trabeculae of new bone form an arch or complete circle about an area of edematous connective tissue This is usually found in lesions of the long bones, and is less common in those of the ribs. It may be linked to the probability that the lesions, in the bones of the extremities are somewhat older when discovered, and hence the trabeculae are larger The production of this fibrous bone under normal and various pathologic conditions has been extensively studied by Weidenreich.

Occasionally the connective-tissue cells, after rounding up apply themselves to the periphery of the metaplastic bone as osteoblasts. Associated with these may be large multinucleate cells, osteoclasts, which appear to break down the newly formed bone. Occasionally this osteoclastic removal of bone leads to the formation of small cysts.

While metaplastic bone formation is a prominent feature of fibrous dysplasia, there are sometimes large areas in which no such osseous transformation of connective tissue is evident. No histologic differences are apparent between this connective tissue, which exhibits no tendency to form bone, and that which does. It is noteworthy however that osseous metaplasia is more

evident at the periphery of the lesions, that is to say in regions adjacent to pre-existing bone. Islets of cartilage are not noted, as a rule.

Thannhauser believed that the connective-tissue pattern of fibrous dysplasia was that of neurofibroma. However by special stain no nerve fibers are found. Some authors have tried to classify the lesions as fibromas. True fibromas of bone do occur but they resemble those found in fascia and in the stroma of various organs and do not contain the bone spicules found in fibrous dysplasia (Fig. 344) They are definitely encapsulated, are separated sharply from the bone and bone marrow and do not blend with the osseous structures after the fashion of fibrous dysplasia. Nor do they contain cystic areas. The recent tendency of Jaffe and Lichtenstein and Schlumberger to include ossifying fibromas in the category of fibrous dysplasia is open to question These lesions of the skull and jaws are, as a rule, isolated, discrete, solitary tumors that tend to evolve from ossifying fibromas to spongy osteomas and thence to eburnated osteomas, an evolution which is not characteristic of fibrous dysplasia. There are, however occasional cases of so-called ossifying fibromas of the jaw occurring in children, which involve both upper and lower jaws or a single jaw diffusely and which are apparently cases of fibrous dysplasia.

Fibrous dysplasia of bone is seemingly a true dystrophy in which the tendency of the mesenchyme to normal ossification is blocked or prevented by a fundamental local disturbance yet to be demonstrated. It bears the same relationship to normal bone with a feeble attempt at osteogenesis fracture bears to normal callous formation. It is apparently a process of fibrous repair in bone which is substituted for true re-ossification. This connective tissue replacement of the marrow cavity and its cancellous bone with a feeble attempt at osteogenesis is not peculiar to fibrous dysplasia although it is the outstanding feature of the disease. It is also seen in such diffuse skeletal diseases as brittle bones, in phases of osteomalacia and in rickets.

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13

Benign Giant-Cell Tumor—Osteoclastoma

CLINICAL FEATURES

Benign giant-cell tumor is a disease of cancellous bone in adults which destroys bone and expands and perforates the overlying cortex. It differs from the solitary bone cysts to which it is closely related in that it has a shorter duration of symptoms and a greater tendency to progress and is associated with the epiphysis rather than with the metaphysis of the shaft. Forty per cent of all cases of giant-cell tumors occur in the third decade of life (Chart 8 p. 246) The sites most commonly involved are the epiphysis of the lower end of the femur and the radius and of the upper part of the tibia (Figs. 209 241) Although giant-cell tumors are typically benign, recurrence after surgical treatment is not rare and scattered reports in the current literature suggest the possibility of metastases, particularly after repeated postoperative irradiations.

The usual clinical history given by these patients has a sequence of trauma, pain, tumor and fracture extending over a period of from 2 to 14 months. In some cases in which roentgenograms have been taken immediately after the injury and at intervals thereafter the gradual development of the areas of bone destruction can be traced. These cases furnish strong evidence of the etiologic role played by injury for they show that the trauma took place prior to the development of the defect in the bone. Pain in these cases is usually severe and of a constant nature and is sufficient to cause disability. The tumor develops rapidly and soon attracts the attention of the patient. Pathologic fracture occurs in about 14 per cent of the cases.

ROENTGENOLOGIC DIAGNOSIS

The roentgenograms of this tumor emphasize its bone-destructive character (Figs. 204-207) The lesion generally assumes an asymmetrical position in an epiphysis, a comparison of early and late lesions indicating that the bone destruction begins subcortically and extends to a more central position at the expense of cancellous bone. The expanded bony shell is extremely thin and in a majority of cases it is soon perforated. Trabeculae, similar to those found in bone cysts, may traverse the tumor but they disappear as the lesion advances. Despite the frequency with which these growths occur in the ends of the bone, extension into the joint cavity is extremely rare, although invasion of the soft parts is not uncommon. In even relatively advanced cases of giant-cell tumors, the bone shows no periosteal reaction, a point which is important in distinguishing these tumors from the osteolytic form of osteogenic sarcoma.

The adult age of the patient and the involvement of an epiphysis of a long bone are the most important aids in making a differential diagnosis. The other common central bone-destructive lesion occurring in an adult is a single focus of metastatic car

cinoma. These metastatic lesions are to be distinguished from giant-cell tumors by their tendency to be located in the shaft at the site of the nutrient vessels rather than in an epiphysis. They do not have the asymmetrical location of the usual giant cell tumor nor so great a tendency to expand the bone.

tions from the capsule. These are trabeculae seen in the roentgenogra and under the microscope they are fibr septa resembling those of osteitis fibr At times, the tumor tissue is white, f and cellular in appearance and relati free from hemorrhage.

The tumor mass is sometimes enc



FIG. 204. (No 25778) (A) anterior and (B) lateral roentgen views of a giant-cell tumor in the upper end of the tibia. Note the asymmetrical location of the lesion and the extreme thinness of the bone shell. The trabeculae have almost disappeared.

GROSS APPEARANCE

The gross specimen of the typical giant cell tumor shows the same bone destruction featured in the roentgenograms but demonstrates more clearly the limited but definite healing reaction about the margin The gross appearance of the tumor is usually hemorrhagic. As Bloodgood stated, it is usually like an old bruise, every shade from red to black, although occasionally it is of a uniform gray putty color At the operation, when touched, it bleeds, oozing like a sponge. When crushed, it is friable like cheese. Fibrous areas may be palpated in the gross, extending inwardly like parti

sulated by fibrous tissue, resembling many respects the leathery fibrous cap of the bone cyst. In the gross, the reac of fibro-ostosis is most pronounced on shaft side. Here the cortical bone thic and extends downward from the shaft ward the epiphysis, preceded by fib tissue. The cancellous bone in the me lary cavity on the shaft side also lays d a fibrous barrier to the tumor and form a capsule visible in the gross, more often discernible only under microscope when sections are made f this region.

In the epiphysis, in which the tum



Fig. 205 (No 32277) (A) anterior and (B) lateral roentgen views of a giant-cell tumor in the upper end of the tibia The bone shell is still intact, trabeculae are present.



Fig 206. (No. 37708) Giant-cell tumor in the lower end of the right radius. The bone shell is perforated on the lateral side, and the trabeculae there are disappearing

situated the margins present contrasting reactions. Because of its asymmetrical position, the tumor borders on cortical bone on its outer side in early lesions while, inwardly, cancellous bone is infiltrated. The border of cortical bone resists longer and more effectively the advances of the tumor. Its reaction consists in laying down new bone and fibrous tissue (Fig. 208). Normally cortical bone, however, is extremely thin in this region, as will be seen from Figure 209, and perforation is by no means rare. The superiority of cortical defense over cancellous bone is demonstrated, nevertheless, by the fact that the tumor expands centrally to the opposite side of the epiphysis in most instances before the cortical shell gives way. The joint cartilage to which the lesion generally extends because of its epiphyseal location, resists successfully the invasion of the joint cavity. Its defense is by means of calcification of its already compact substance, the calcified tissue being transformed into bone (Figs. 210–211).

Thus it will be seen that everywhere about the tumor normal structures are reacting to stem the invasion. When this reactive tissue is examined microscopically it shows a histologic structure typical of the fibro-ostosis seen in the wall of the bone cyst. Indeed the microscopic structure of the giant-cell tumor differs from that of the bone cyst, not in kind but in degree. Here there is a preponderant fibrous proliferation and new bone formation with little or no remnant of giant-cell tumor tissue. Microscopically these giant-cell areas represent the fundamental pathologic change underlying these lesions, and a careful



FIG. 207 (No. 37360) (A) roentgenogram, and (B) gross specimen of a pathologic fracture through a giant-cell tumor in the lower end of the femur. Fracture has aided the tumor in the invasion of the soft parts.

study of them discloses the nature of giant cell tumor

MICROSCOPIC FEATURES

The tumor is composed of large, multinucleated giant cells embedded in a mass of smaller round and spindle cells (Fig 212) The giant cells average over 30 per field under the low power with the number of nuclei in each cell varying from 15 to 200 The cells range in size from 10 to 100 microns and may or may not have distinct borders to the cytoplasm.

The number of giant cells present varies from field to field, being more numerous about areas of hemorrhage, about spicules of old bone or about the walls of minute cysts. The typical giant-cell tumor however maintains with remarkable regularity in most areas, a crowding of large, multinucleated elements. Giant cells with few nuclei, relatively small and sparcely distributed, are not typical of the benign giant-cell tumor but are more characteristic of the variants of osteitis fibrosa and osteogenic sarcoma (Figs. 213 and 214)



FIG. 208. (No 32924) (A) gross specimen, and (B) microscopic section of a giant-cell tumor in the lower end of the fibula. The photomicrograph shows a reaction of new bone and fibrous tissue in the tumor capsule. The new bone has taken on a deep stain.

An outstanding peculiarity of the typical giant-cell tumor is the cellular stroma in which the giant cells are embedded. Two kinds of cells can always be found in this stroma, the round and the spindle cell, but in the typical giant-cell tumor group, the round cells outnumber the spindle cells in every instance. This small round cell has a relatively large nucleus and a small amount of cytoplasm. There is a definite

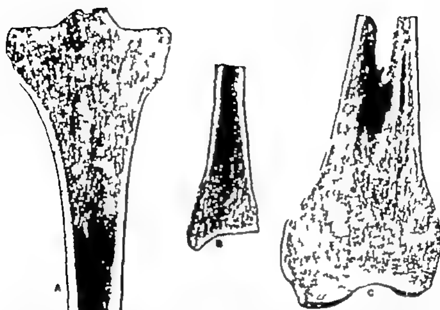


Fig. (After Toldt) The epiphyseal regions (most commonly affected by giant-cell tumor) (A) upper part of the tibia, (B) lower part of radius and (C) lower part of femur Attention is directed to the normal cancellous structure of the epiphysis and the thinning of the cortex and periosteum in these regions.

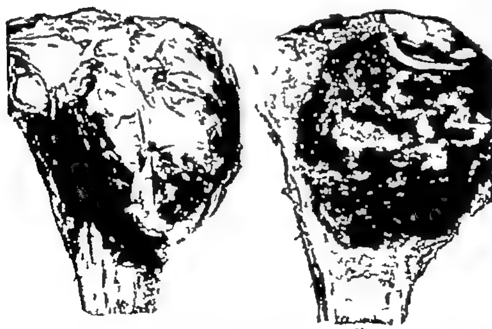


Fig. 210 (N 27001) Giant-cell tumor in the upper end of the tibia. The tumor extends to the joint cartilage. No fibrous reaction is discernible here in the gross on the cut surface. Fibrous tissue may be seen overlying the outer surface of the tumor on the uncut surface.

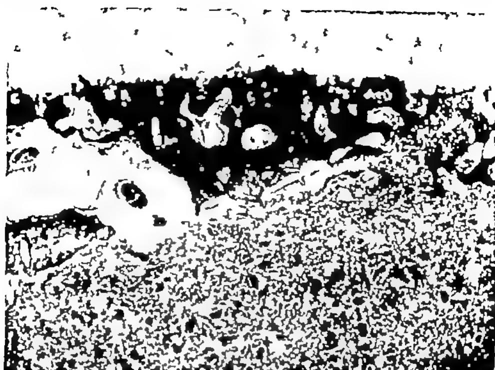


Fig. 211 (No. 10975) Photomicrograph showing the reaction of joint cartilage. The cartilage has become calcified and is laying down compact bone to resist the invasion of the giant-cell tumor

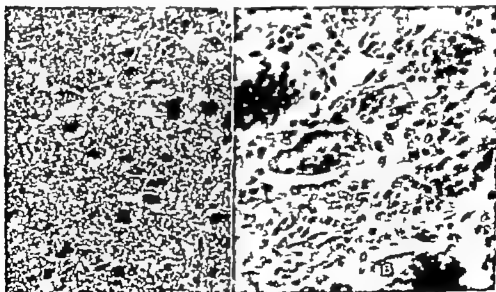


Fig. 212. (No. 37360) (A) low and (B) high-power photomicrographs of the *typical giant-cell tumor There are over 30 cells to the low power* field and the usual number of nuclei is over 15 per cell. In the high-power it will be seen that round cells predominate in the stroma. Compare Figure 212 with Figures 213 and 214

nuclear wall and a nucleolus. The nucleus is generally from 3 to 7 microns in size with a fairly large amount of chromatin evenly distributed, and the borders of the cytoplasm are usually indistinct

portant variation is the tendency for the giant cells to have a more acidophilic cytoplasm with occasionally a greater concentration of chromatin in the nuclei and other signs of early degeneration. This

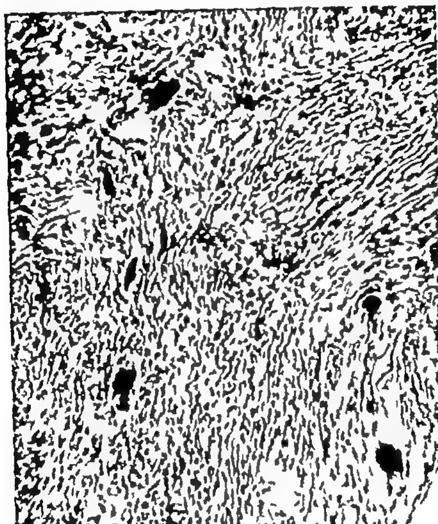


Fig. 213. (No 32013) The giant-cell variant of osteitis fibrosa. Note the small size and scarcity of the giant cells and the large number of spindle cells and fibroblasts in the stroma. Microscopically the tumor is benign.

could be accounted for by the age of the giant cell, the inference being that the giant cells are formed by agglutination of the smaller cells in the stroma.

There is, apparently a definite relationship between the plump spindle cell of the stroma and the giant cell. In the first place, when the giant cells predominate in the tumor the small spindle cell prevails in the stroma. Moreover the nuclei of the giant cell always have the same general form and staining characteristics as the nuclei of the stromal cells. The only im-

Hemorrhage is conspicuous in the histologic structure of giant-cell tumor Red blood cells in a well preserved state are scattered through the tumor more often unenclosed than enclosed by endothelial

walls. The *typical giant-cell tumor is thus* both hemorrhagic and vascular newly formed vessels being by no means rare. Area of organizing hemorrhage are frequent, and bordering on these is loose gins, the frayed and worn edges, and the small size of the bone cells included in the matrix of the spicules. Other spicules with osteoblasts applied to their surface are new bone resembling that frequently seen in so-

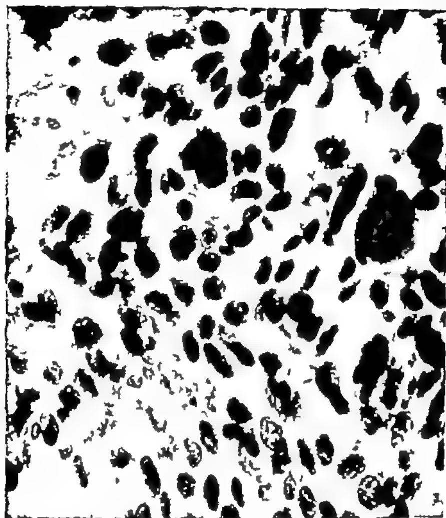


FIG. 214. (No 39274) Osteogenic sarcoma with giant cells. Two giant cells are present in the field, each having less than 15 nuclei. The most important diagnostic feature of the section is the presence of the large vesicular nuclei, some of which are undergoing mitotic division. (Compare with Figure 212.)

edematous tissue intermingled with areas like those seen in benign cysts.

Spicules of bone are frequently found near the margin of the tumor or its capsule. Some of these spicules are undoubtedly surviving portions of old bone undergoing destruction and are recognized by the giant cells applied to their surface, the condensation of calcium salts at the mar

called osteitis fibrosa, and represent a healing reaction rather than bone of tumor origin (Fig 234)

The spindle cells about the new bone spicules are found elsewhere in the tumor among the round cells of the stroma. They are oval and slender in form with a nucleus rather well defined and a cytoplasm elongated but not abundant, without definite



FIG. 215 Roentgenograms showing giant-cell tumors in unusual locations. (*Left*) (No. 46694) Giant-cell tumor of the astragalus. There is destruction of the spongiosa of the astragalus, which has led to partial collapse (*Right*) (No. 46472) Giant-cell tumor of the midphalanx of the ring finger

outlines. Fine fibrils surrounding these spindle cells indicate their fibroblastic tendencies and identify them as the type of cells seen in the wall of benign cysts.

The Relation of the Histogenesis of Intracartilaginous Ossification to Giant-cell Tumor Although works on embryology since 1890 (Quain) give the histogenesis of the long bones in some detail, the importance of this process for giant-cell tumor makes a reconsideration of the whole process advisable. For this purpose there was available a most valuable collection of human embryos in the Carnegie Institute of Embryology This collection was placed at our disposal through the courtesy of Professor Streeter director of the institute.

In the long bones, the process of osteogenesis is alike in both the shaft and the epiphysis, the two being formed by intracartilaginous ossification. There are usually three centers of ossification, one for the diaphysis and one for each epiphysis. The center of ossification of the shaft develops first, new bone extending in two directions toward each metaphysis. The two epiphyseal centers develop much later (Fig 9 Chap. 1) Hence, the areas in which new bone formation persists in the child and the young adult are in the metaphyses of the bones on the shaft side of the epiphyseal line and in the epiphyses. As we have seen, these persisting centers of ossification are the sites where bone cysts and giant-cell tumors develop The histologic processes going on in these regions or centers explain how these growths arise.

The new bone is preformed in cartilage and later replaced by permanent bone. This process may be said to take place by transformations occurring in three stages (1) the calcification of cartilage to form primary areolae (2) the invasion and resorption of the areolae and their walls (3) the laying down of permanent perichondral bone. Both longitudinal and transverse sections are necessary to a clear conception of these three stages, and both are illustrated here and in Chapter 1 (Figs. 219 and 220) In the longitudinal sections the ends of the bone are still primitive cartilage. Toward the center of the shaft, the cartilage cells line up in rows, enlarge and

Schafer E. A., and Thane, G D Quain's Elements of Anatomy ed. 10, 1891, Vol. I, Part 2, pp. 263-254.

secrete an increased hyalin matrix which becomes calcified to form a honeycombed structure. The cartilage cells within these calcified compartments next shrivel and atrophy their nutrition being cut off by the calcified walls which form the primary areolae All this occurs in the regions that termed by us angio-spongiosa It is best seen in cross sections taken from the long bones of young human embryos. It is just this phase that is most poorly described in the textbooks, and the cross sections illustrated here are usually omitted. In the transverse sections it will be seen that the pri-



FIG. 216 (No 55092) Giant-cell tumor of the wing of the ilium. The tumor has eroded the sacro-iliac joint.

are to be the future medullary cavity In the subperichondral region (what is to be subperiosteal) along the margins of the shaft, osteoid tissue is being laid down by the perichondrium. In the next stage, this perichondral osteoid tissue is perforated by blood vessels that proceed inwardly to the primary areolae (Fig 221)

This stage in which the calcified areolae are invaded by blood vessels and resorbed is the most significant phase for the under standing of giant-cell tumor and has been mary areolae are invaded by buds of tissue proceeding from the outlying mesenchyme surrounding the perichondral bone. The manner in which these buds perforate the perichondral bone, invade the calcified areolae and absorb them is most important. Mesenchymal cells collect, their nuclei darken and the cells agglutinate to form giants cells or osteoclasts. These giant cells are first to perforate the perichondral bone (Fig 218) and the first to force entrance into the compartments of the calcified

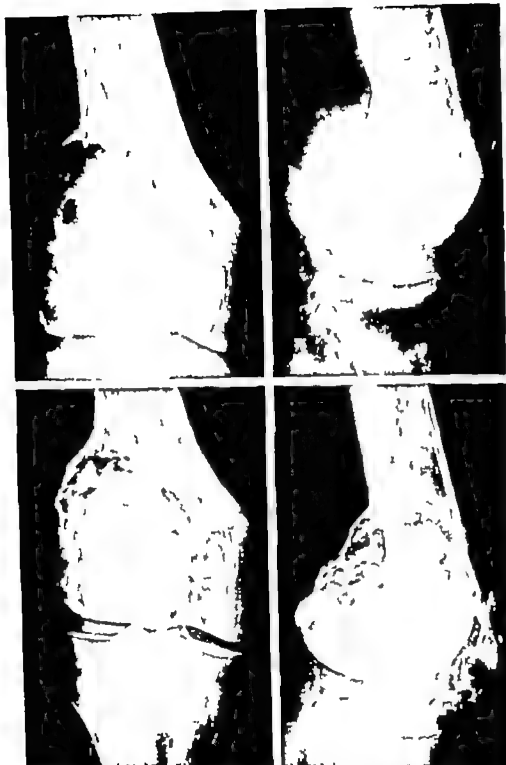


FIG. 217 (No 61772) Roentgenogram of a giant-cell tumor of the lower end of the femur (*Top*) Giant-cell tumor of the lower end of the femur before irradiation, in 1941 (*Bottom*) Roentgenogram showing the same lesion following irradiation, in 1943. Repeated irradiation of giant-cell tumor is not advised because sarcoma subsequently develops in some of these irradiated cases.

areolae. In their wake come newly formed capillaries, osteoblasts and other mesenchymal elements. When the stage of resorption of calcified cartilage is at its height, and the medullary cavity is being formed, a cross section of a young bone of an embryo of from 90 to 100 mm., taken from this region will show a veritable giant-cell tumor. The cavity of the bone will be filled with giant cells, round cells, small blood vessels, hemorrhage, fibroblasts and osteoblasts. Later the osteoblasts persist near the margin of the medullary cavity to aid in the formation of cancellous and then compact bone while the marrow cavity itself becomes filled with young marrow elements.

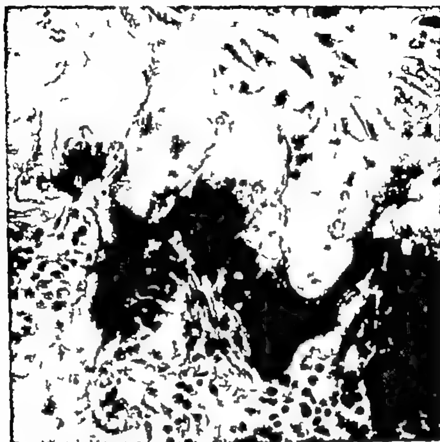


FIG. 218. (No 40936) Three primary areolae formed by calcified cartilage with a portion of two others are shown in the photomicrograph. One areola is still intact, and in it two degenerating nuclei of cartilage cells are seen. In the other areolae giant cells are seen forcing their entrance through calcified cartilage. Note that the nuclei of the giant cells are entirely different in morphology from those of the degenerated cartilage cells, and that they outnumber the cells in the calcified area. This disproves the statement of Arey that giant cells are rarely seen when calcified cartilage is undergoing resorption and that the giant cells are formed as a by-product of degenerated dissolving bone by the agglutination of the nuclei of old bone cells.

These embryologic studies emphasize the association of giant cells with the performation of new perichondral bone and the resorption of calcified cartilage. The specimens show clearly that the giant cell proceeds inwardly from outside of the shaft of the bone and that these multinucleated

elements may arise in the primitive periosteal tissue It is not necessary to assume that they arise from the marrow reticulum as many histologists believe (Maximow) nor that they are derived from the endothelium of capillaries. The only distinct evidence is in favor of the view that they are formed from primitive mesenchyme and that such mesenchyme exists in the early stages of osteogenesis periosteally

Giant-cell formation, therefore, marks the beginning of bone perforation in the embryo, and in the wake of these cells new blood vessels and osteoblasts follow Over and over again in both giant-cell tumor and osteitis fibrosa, particularly of the polycystic variety we have observed giant cells on the outside of new blood vessels and vascular spaces (Figs. 225 and 228) showing that the giant cells in these lesions retain the same histologic function as the osteoclasts seen in human and other mammalian embryos.†

Turning now to the consideration of giant-cell tumors, the location of these lesions (and also their healing form, bone cysts) at the sites and at the ages when intracartilaginous bone is being formed relates them to this process. The bone cyst occurs on the shaft side of the epiphyseal line in children, where the transformation of calcified cartilage to bone proceeds most rapidly during youth. The giant-cell tumor occurs in the epiphysis of adults where the transformation of calcified cartilage to bone proceeds slowly but progressively after adulthood is reached. More specifically and convincingly the bone-destructive character of these lesions and the prevalence of giant cells or osteoclasts in them relate them to the process of resorption of temporary bone characterized by the proliferation of osteoclasts or giant cells which has been described in the foregoing review of the histogenesis of long bones. From this we conclude that the giant-cell tumor and the related lesion of bone cyst are the result of an abnormal hyperplasia of osteoclasts preceded by a normal stage in which osteoclastic proliferation is taking place as a phase in the histogenesis of intracartilaginous bone.* From this point of view the term progressive osteoclasia is suggested for the process underlying the giant-cell tumor and the term regressive osteoclasia for bone cysts. These terms show their relationship one to the other and also to the normal process of osteoclastic proliferation in the histogenesis of the long bones.

GIANT-CELL TUMORS OF THE JAWS

The validity of the hypothesis which relates giant-cell tumor to the resorption of temporary bone or calcified cartilage is to be proved by the facts in regard to these tumors wherever they occur In giant-cell tumors and bone cysts of the long bones this conception holds, for by age incidence location and histologic structure these lesions are related to osteogenesis via cartilage However tumors of the giant-cell variety occurring in the jaws, along the alveolar border in the form of the giant cell epulis, and in tendon sheaths and soft parts, offer greater difficulties in the establishment of their relationship to the resorption of temporary bone

The Chondrocranium in Relation to Giant-cell Tumors of the Skull If the intimate association of the pathologic changes in

Maximow A. Untersuchungen uber Blut und Bindegewebe Arch. f. mikr Anat. 76 1 1910

† That this same histologic function of the osteoclasts as forerunners of the vascularization and resorption of temporary calcified structures holds for repair processes and even for foreign bodies is shown by the experiments of Pollock, W E., et al., on The viability of transplanted bone (Arch. Surg. [illegible] 607 1929) Here in experimental bone transplants it was found that giant cells attacked the transplanted bone preliminary to its vascularization and the formation of new bone.

* That the giant cell is active and living rather than an agglutination of dying cells has been demonstrated in human tissue cultures by Dr. G. O Gey In motion pictures made of these cultures prepared from giant-cell tumors the activity of the giant cells may be observed.



FIG 219 (No 32922) Roentgenogram of giant-cell tumor of upper end of humerus. This giant-cell tumor is arising in the greater trochanter The lesion healed under repeated irradiation over a period of several years The patient, however ultimately succumbed to agranulocytosis.

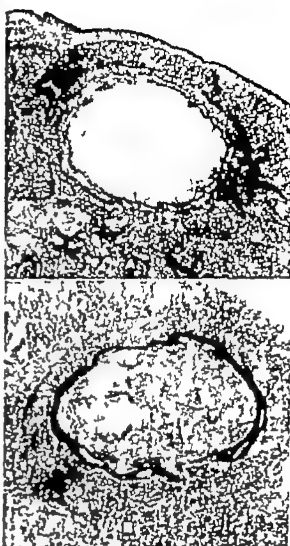


FIG 220 (No. 40934) Cross-sections of the humerus of a human embryo of 90 mm The upper section (A) shows the perforation of the perichondral osteoid tissue by mesenchymal elements at numerous points proceeding inwardly from the primitive periosteum. The calcified cartilage is about to undergo resorption by these invading mesenchymal elements. (B) is a section near the region of the midshaft of the same bone showing a more advanced stage in the resorption of calcified cartilage by mesenchymal elements and the formation of the marrow cavity Note how the subperichondral osteoid tissue has been broken through at different points. (Sections furnished through the courtesy of Dr Streeter of the Carnegie Institute of Embryology)

giant-cell lesions to the resorptive process in cartilaginous bone is true, then the bones of the skull and face should furnish valuable evidence to support it. For it is known that certain bones of the skull—particularly the frontal, parietal and tabular portion of the occipital—which compose the calvarium are formed from membrane rather than cartilage, as are most of the bones of the face. These bones should not be directly involved by either bone cysts or giant cell tumor It is true that they are provided with periosteum and that this tissue retains osteoclastic as well as osteoblastic potentialities, but in such instances, the lesion should be periosteal instead of central and present other peculiarities. A review therefore, of the exact histology and location of giant-cell tumors of the head becomes of special significance.

Excluding the epulis of the alveolar border the records of the surgical pathologic laboratory of the Johns Hopkins Hos-

TABLE 20 GIANT-CELL TUMORS

Pathology No.	Race	Sex	Age	Location	Duration, mos.	Symptoms	Fracture	Treatment	Results of Treatment
66187	W	F	35	Femur, lower	6	Pain	[illegible]	Curettage	Well 9 yr
62496	W	[illegible]	33	Femur, lower end	5	Trauma	0	Curettage	Lost
62464	W	M	[illegible]	Tibia, upper end		Trauma	0	Recurrence roentgen therapy	Well 4½ yr
62436	W	M		Tibia, upper end	20	Trauma	0	Amputation	Well 5 yr
62431	W	F	[illegible]	Metaphysis, left femur	6	Trauma	0	Curettage	Well 5 yr
62440	W	M	[illegible]	Acromion left clavicle		Trauma	0		Lost
62104	W	M		Proximal phalanx middle finger			[illegible]	Amputation	Well 6 yr
61812	W	M	14	Tibia, lower		Trauma and pain	0	Curettage	Well 5 yr
61772	W	M	31	Femur, lower end		Trauma	0	Curettage and irradiation	Lost
61704	W	F	56	Radius, lower end	6	Pain	0	Excision	Lost
61660		F		Tibia, upper end			0		Lost
61604		F		Tibia, lower end		Pain	0	Operation	Lost
61540	W	M	[illegible]	Femur, lower end	4	Pain and tumor	0		Lost
61294	W	M	23	Femur, lower end	3	Trauma	0	Amputation	Well 6 yr
60746	W	M	30	Astragalus	5	Trauma	0	Curettage	Well 7½ yr
59948	W	F	16	Tibia, upper end			0	Curettage	Well 8 yr Lost
59614	W	F	60	Ilium, left wing	24	Pain	0	Irradiation	Dead 6 yr
59584	W	M	26	Femur, lower end		Trauma	0	Amputation	Well 10 yr
59426	W	M	34	Femur, lower end	8	Pain	0	Curettage	Well 9½ yr
59379	W	F	24	Ilium, left wing	20	Pain and trauma	[illegible]		Lost
59232		M	20		9	Tumor and pain	0	Amputation	Well 8 yr
58728	W	M	29	Tibia			[illegible]	Curettage	Well 2 yr Lost
58490	W	M	21	Femur, lower end	11	Pain tumor	0	Irradiation	Well 3 yr Lost
58402	W	M	[illegible]	Radius, lower end		Trauma	0	Curetted twice	Well 11 yr
58340	W	M	12	Ulna, upper	30	Trauma	0	Irradiation	Well 10 yr Killed in war
58116	W	F	30	Ulna, lower end	4	Trauma	0		
57812		M	[illegible]	Patella	18	Trauma	[illegible]		
57414	W	M	25	Tibia	10		0	Surgery	
57275	W	M		Tibia				Curettage	Well 1 yr
57126	W	F	34	Tibia	18		[illegible]	Amputation	Well 1 yr
57118	W	F	26	Scapula, right acromion		Pain	0	By roentgen rays	Lost
56388	W	F	adult	In front of 3d–6th cervical vertebra				Curettage	Well 12 yr
55672	W	M	10	Femur, lower end	20	Trauma	0	Curettage	Lost
55226		M		Tibia, upper end			0	Curettage	Well 12 yr
54842	W	M	46	Fibula, left	6		[illegible]	Curett	Well 2 yr
54408	W	F	[illegible]	Radius	2		0	Irradiation	Well 3 yr
54000	W	F	53	Femur, lower end	[illegible]	Pain	[illegible]	Biopsy irradiated	Well 4 yr
53870	W	F	53	Femur, lower end	3	Pain	Yes	Amputation	Dead immediately
53816		F		Sacrum			[illegible]	Curettage	Dead 4 yr
53642	W	M	41	Femur, right	8		0	Amputation	Well 5 yr
53528	W	M	46	Femur, right	1		[illegible]	Amputation	Well 3 yr
52922	W	F	43	Humerus	8	Paresthesia	[illegible]	By roentgen rays	Dead 2 yr (agranulocytosis)
52786	W	F	33	Femur, lower end	8	Pain	[illegible]	Curettage	Well 5 yr
52696	W	M	3	Back	6		0	Irradiation	Well 4 yr
51966		F	[illegible]	Ilium at acetabulum, left	4	Pain	0	Curettage	Lost

TABLE 29 GIANT-CELL TUMORS (*Continued*)

Pathologic No.	Race	Sex	Age	Location	Duration, mos.	Symptoms	Fracture	Treatment	Results of Treatment
51690		M	31	Femur lower end	30	Trauma	0	Osteotomy 1932 Amputation, 1938	Lost 1940 Well 9 y
51586	W	M	23	Rib			0	Irradiation	Well 2 y
50002	W	F	19	Femur	24		0	Irradiation	Well 6 yr
49942	W	F	23	Femur lower end	2	Pain	0	Curettage and amputation	Well 9 y
49142	W	F	37	Knee	5		0	Curetted	Well 7 yr
48766	W	F	40	Cuneiform bone	24		0	Curetted	Well 14 y Lost
48364	W	F	20	Ulna	36		0	Curettage	Well 5 y
48186	W	F		Radius, left	2½		0	Curettage	Well 3 y
47833	W	M		Femur left	4		0	Surgery	Well 5 yr
47768		M	31	Femur lo er end	3	Pain	Yes	Curettage, biopsy	Well 14 y
47828	W	F	30	Femur			0	Biopsy	Well 4 yr
47396	W	M	25	Tibia, upper end	16	Trauma	0	Curettage	Lost
47312	W	F	50	Radius, right	5		0	Curettage	Well 6
47030	W	F	20	Femur lower end		Pain	0	Curettage	Well 16 y
46732		F	32	Patella			0	Curettage	
46694	W	F	27	Astragalus	36	Trauma	0	Excision	Lost
46570	W	M	[illegible]	Humerus	½		0	C rettage	Dead 3 yr
46472	W	M	31	Finger	3		0	Amputation	
46218		M	40	Femur lower end			0	Amputation	Well 9 yr
45883	W	M	27	Tibia			0	Curettage	Well 5 yr
45508	W	M	[illegible]	Femur right			0	Curettage	Well 7 y
45116	W	F	71	Femu			0	Irradiation	Dead 2 yr
45096	W	M	40	Tibia, right		Trauma, pain	0	C rettage, by roentgen rays	Well 15 yr
45090	W	F	30	Femur lower end	4	Trauma	0	Curettage	Well 6 yr
44720	W	M	28	Femur	12		0	Amputation	Well 10 yr
43740	W	M	28	Radius	15		0	Irradiation	Well 6 yr
43960	W	F		Radius			0	Irradiation	Well 6 y
43908	W	M	32	Radius	24	24	0	Curettage	Well 10 yr
43886	W	F	17	Tibia			0	Curettage	Well 6 y
43128	W	M	37	Tibia			0	Surgery	Well 7 yr
41704	W	M	36	Radius	4		0	Curettage	Well 7 yr
41610	W	M	17	Scapula			0	Curettage	Well 9 yr
41338	W	M	38	Vertebra			0	Curettage	Well 11 yr
41234	W	M	16	Humerus	24		0	Curettage	Well 11 y
40486	W	M	21	Hand			0	Surgery	Well 12 yr
39860	W	M		Radius			0	Curettage	
39750	W	F	18	Shoulder	12		0	Curettage	Well 14 yr
38845	W	F	30	Radius	2		0	Curettage	Well 11 y
38216	W	M		Radius			0	Curettage	Well 10 y
38134	W	F	40	Tibia			0	Surgery Irradiation	Well 6 y
37000	W	M	4½	Fibula			0	Curettage	Well 1 y

pital extending over a period of 35 years showed only 22 cases of giant-cell tumor occurring in the head. Bone cysts did not occur in this locality. Two of the giant cell tumors were found in the temporal fossa, 6 were recorded in the upper and 14 in the lower jaw. In the purely membranous portion of the calvarium (the frontal and parietal bones) not a single instance of these lesions is recorded (Tables 32 and 33). The three sites of the lesions, the temporal fossa, the upper jaw and the mandible, it is true, are in regions of membranous bone. The squamous portion of the temporal bone the superior maxilla and a large portion of the mandible are formed from membrane. But there are also cartilaginous centers of ossification in the neighborhood of the temporal fossa, the maxilla and the mandible.

Table 3 from Jordan and Kindred* summarizes the essential points in the his-

* Jordan, H. E., and Kindred, J. E.: A Textbook of Embryology. New York, Appleton, 1926.

togenesis of the chondrocranium. The same information is given diagrammatically in Figure 222. Here the portions of the skull derived from cartilage are represented by areas in black, and in Figure 223 the associated with the wing of the sphenoid (which is derived from cartilage) projecting into this locality. These facts are further substantiated by the data in Table 32. In this table it is seen that in the mandible



FIG. 221 (No. 40934) Higher magnification of the section shown in Figure 220. The photomicrograph illustrates the first step in the resorption of calcified cartilage. A giant cell proceeding from the primitive periosteum is perforating the perichondral osteoid tissue and attacking the primary areolae. In its wake is shown a small blood vessel and other mesenchymal elements arising from the primitive periosteum. The picture disproves the assumption by numerous embryologists that the giant cells of an osteoclastic nature are formed from the reticulum in the marrow cavity, for here we see that the giant cell is entering the future marrow cavity from the periosteum outside of the bone.

twenty-two lesions occurring in the skull have been plotted according to location. It will be seen at a glance that the giant-cell tumors in the lower jaw, which is the most frequent site of these tumors of the skull, coincide in locality with centers of intracartilaginous ossification for the mandible. The two lesions in the temporal fossa are most of the giant-cell tumors occur at the symphysis where Meckel's cartilage participates in the formation of this bone. The others are located at the ramus where there is a separate center for cartilaginous ossification. Table 33 also correlates the origin of the lesions in the temporal fossa with cartilaginous centers in the sphenoid bone.

Table 30. Typical Giant Cell Tumor

Path. N	Race	Sex	Age	Location	Symptoms	Fracture	Treatment	Roentgen Findings	Microscopic Appearance	Results of Treatment
43166	W	F	37	Femur lower end		0	Curetting		Typical giant-cell areas	Discharged well
43119		F	14	Radius, shaft and upper end		0	Resection	Bone shell intact	Fibrous reaction at capsule	Discharged well
42430	W	F	18	Tibia, right lower end		0	Curetting		Typical giant-cell areas	Discharged well
40542	W	M	22	Tibia, left upper end	Tumor 1½ years	0	Curetting	Bone shell intact	Typical giant-cell areas	Well 13 years
40163		M		Radius, lower end		0	Curetting		Typical giant-cell areas	Well 13 years
[illegible]	W	M	22	Tibia, upper end	Tumor 6 months	0	Curetting	Bone shell intact	Typical giant-cell areas	Amputated, well 12 years
[illegible]	W	F	25	Femur, right lower end	Pain 3 years	8 mos	Roentgen	Bone shell intact		Well less than 5 years
[illegible]	W	F	15	Scapula, left, neck	Pain	0	Curetting	Bone shell intact		Well less than 5 years
[illegible]	W	M		Ulna, right lower end	Trauma 3 months	0	Curetting		Fibrous reaction at capsule	Well 8 years
[illegible]	W	F		Femur lower end		yes				Well less than 5 years
[illegible]	W	F	24	Radius, left lower end	Tumor 7 weeks	0		Bone shell intact		Discharged well
[illegible]	W	F	28	Femur, lower end, left	Trauma 5 months	0	Curetting	Bone shell intact		Well 11 years
[illegible]	W	M	22	Tibia, left upper end	Trauma 8 months	0	Curetting	Bone shell perforated	Typical giant-cell areas	Discharged well
[illegible]	W	M	12	Femur head	Tumor	0	Exploration		Typical giant-cell areas	Discharged well
[illegible]			21	Humerus, right upper end		0		Bone shell intact		Discharged well
[illegible]	W	F	23	Femur, right lower end	Pain 8 months	6 [illegible]	Amputation	Bone shell perforated	Typical giant-cell areas	Discharged well
[illegible]	W	F	31	Tibia, left lower end	Pain 9 months	0	Curetting	Bone shell intact	Typical giant-cell areas	Well 18 years
[illegible]	W	F	26	Femur left lower end		0	No operation	Bone shell perforated		Well 10 years
[illegible]		M		Radius, left lower end		yes	Curetting	Bone shell perforated	Typical giant-cell areas	Well 10 years
[illegible]	W	F	22	Tibia, right upper end	Trauma 22 months	0	Exploration	Bone shell perforated		Discharged well
[illegible]	W	F	31	Radius, left lower end	Trauma 6 months	0	Roentgen	Bone shell perforated		Well less than 5 years
[illegible]	W	M	43	Tibia, left upper end	Trauma 15 months	0	Refused	Bone shell perforated		
25784	W	F	23	Fibula, left upper end	Tumor 12 months	0	Amputation	Bone shell intact		Well 10 y
[illegible]	W	M		Tibia, left lower end		0	Curetting	Bone shell intact		Well 10 yr
[illegible]	W	F	18	Femur left upper end		0	Exploration	Bone shell intact	Fibrous reaction at capsule	Well 11 years
23114	W	F	19	Femur lower end	Pain 4 years	0	Curetting			Well more than 5 years
23113	W	F	40	Tibia, upper end		0	Amputation	Bone shell intact		Well 10 years
23103	W	F	30	Tibia, lower end	Trauma 5 months	0	Curetting	Bone shell perforated		Well less than 5 years
23100	W	F	53	Femur lower end		0	Amputation			Died of other causes
[illegible]	W	F	30	Tibia, upper end	Tumor 3 months	0	Roentgen	Bone shell perforated		Well less than 5 years
21970	W	F	7	Tibia, left upper end	Trauma	0	Curetting	Bone shell perforated	Fibrous reaction at capsule	Well 5 years
21874	W	F	26	Ulna, lower end	Trauma 10 months	0	Resection	Bone shell intact	Typical giant-cell areas	Well less than 5 years
21842	W	F	37	Femur upper end	Pain 2 months	yes	Roentgen	Bone shell intact		Discharged well
[illegible]	W	F	17	Tibia, right upper end			Curetting	Bone shell intact		Well 5 years
[illegible]	W	F	14	Femur upper end	Pain 1 year	0	Curetting	Bone shell perforated	Fibrous reaction at capsule	Well 3 years

34004	W	M	36	Femur, right lower end	Pain 15 months	0	Curetting	Bone shell perforated		Well 5 years
33748	W	M	26	Radius, lower end	Tumor 4 months	0	Curetting	Bone shell intact	Typical giant-cell areas	Well 13 yr
33410	W	M	27	Ulna, left lower end	Pain 6 months	Yes	Amputation	Bone shell perforated	Typical giant-cell areas	Well 17 y
33051	W	M	22	Tibia, right upper end	Tumor 8 months		Curetting	Bone shell perforated		Well 5 years
33277	W	M	23	Tibia, left upper end	Pain 2 years	0	Amputation	Bone shell intact	Typical giant-cell areas	Well more than 5 years
32079				Tibia		0	Amputation			Well more than 5 years
31970	W	F	62	Femur, left lower end	Trauma 6 months	0	Curetting	Bone shell perforated	Typical giant-cell areas	Well more than 5 years
31921	W	F	31	Radius, right lower end	Tumor 4 months	Y	Curetting	Bone shell perforated	Typical giant-cell areas	Well less than 5 days
30994	W	F	27	Scapula	Pain 2 years	Y	Resection	Bone shell perforated		Well more than 5 years
30313	N	M	39	Ulna, upper end	Pain 18 months	0	Resection	Bone shell intact		Well 10 years
30248	W	M	14	Radius, lower end	Trauma 6 weeks	0	Curetting			Well 10 years
31047	W	F	23	Femur, upper end	Trauma 6 years	Y	Excision	Bone shell intact		Well more than 5 years
31055	W	M		Humerus, upper end	Trauma 10 months	0	Amputation	Bone shell intact		Well 10 years
30172	W	F	18	Tibia, right upper end	Pain 3 months	0	Excision			Well less than 5 years
30059	W	M	22	Tibia, left upper end	Tumor 3 years	0	Curetting	Bone shell perforated		Well more than 5 years
29718	W	F	24	Femur, lower end		Y	Amputation	Bone shell intact		Well more than 5 years
29716	W	M	22	Radius, lower end	Trauma 8 months	0	Curetting			Well 10 years
29721	W	F	73	Tibia, upper end	Trauma 1 year	0	Curetting	Bone shell perforated	Typical giant-cell areas	Well 10 years
29674	W	F	35	Rib, trunk posterior	Pain 6 years	0	Resection	Bone shell perforated	Typical giant-cell areas	Well 8 years
29419	W	M	29	Tibia, upper end	Trauma 9 years	0	Curetting	Bone shell intact		Well 10 years
29409	W	M	31	Tibia, right upper end	Pain 1 year	0	Curetting	Bone shell perforated	Typical giant-cell areas	Well 10 years
29405	W	F	28	Radius, left lower end	Tumor 6 months	0	Amputation	Bone shell perforated		Well 9 years
29285		F		Humerus, right upper end		Y	Curetting	Bone shell perforated		Well more than 3 years
29 [illegible]		M		Femur, left lower end	Tumor	0	Curetting			Well less than 5 years
29150		M		Tibia, right upper end	Trauma 3 years	0	Refused			No information
28472	W	F	81	Ulna, right upper end		0	Curetting	Bone shell intact		Well more than 5 years
28473	W	M	37	Femur, left lower end	Trauma 1 year	0	Amputation	Bone shell perforated	Typical giant-cell areas	Well more than 3 years
28 [illegible]	W	M	13	Humerus, upper end	Tumor 1 year	0	Curetting	Bone shell intact		Well less than 3 years
28215	W	M	23	Tibia, left upper end	Pain 9 months	0	Curetting		Fibrous reaction at capsule	Well more than 3 years
28107				Tibia, upper end		0	Amputation	Bone shell perforated	Fibrous reaction at capsule	Well 11 y
27497	W	F	25		Tumor 5 weeks	0	Amputation	Bone shell perforated		Well 10 years
27805	W	M	20	Femur, right lower end	Pain 1 year	0	Refused	Bone shell intact		Well more than 5 years
27604	W	F	20	Tibia, upper end	Pain 1 year	0	Resection	Bone shell intact	Fibrous reaction at capsule	Well 10 years
27563	W	M	45	Radius, left lower end	Trauma 10 months	0	Curetting	Bone shell perforated		Well 10 years
27318				Tibia, upper end		0			Typical giant-cell areas	Dead 18 yr, infection
27116	W	F	26	Femur, right lower end	Pain 6 months	0	Amputation	Bone shell perforated	Typical giant-cell areas	Well more than 3 years
27049				Radius, upper end		0	Curetting		Fibrous reaction at capsule	Well more than 3 years
27001	W	M	30	Tibia, left upper end	Pain 18 months	0	Resection	Bone shell perforated	Typical giant-cell areas	Well more than 3 years
26761	W	M	16	Humerus, left upper end	Trauma 10 months	0	Curetting	Bone shell intact	Typical giant-cell areas	Well more than 3 years
26879	W	M	53	Ulna, right upper end	Tumor 1 year	0	Refused	Bone shell perforated		Well less than 3 years
26875		M		Tibia, upper end	Trauma	0	Amputation	Bone shell perforated		Well less than 3 years

TABLE 30 TYPICAL GIANT CELL TUMOR (*Continued*)

Path. No.	Race	Sex	Age	Location	Symptoms	Fracture	Treatment	Roentgen Findings	Microscopic Appearance	Results of Treatment
25909	W	F	26	Tibia, upper end	Pain	0	Curetting	Bone shell intact	Typical giant-cell areas	Well more than 5 years
25779	W	F	24	Femur, right lower end	Trauma 2 years	Yes	Refused	Bone shell perforated		Well more than 5 years
24797	W	F	32	Radius, left lower end	Tumor 1½ years	0	Resection	Bone shell intact		Well 5 years
24124 }				Ulna, lower end		0	Resection			Well more than 5 years
23432	C	F	21	Ulna, right lower end	Tumor 1 year	0	Resection	Bone shell perforated	Typical giant-cell areas	Well less than 5 years
21822	C	F	34	Fibula, right lower end	Tumor 6 years	0	Curetting	Bone shell perforated		Well 10 years
20373 }	W	F	41	Femur, left lower end		0	Amputation			Well 10 years
20118	W	M	46	Femur, right lower end		Yes	Amputation	Bone shell perforated	Typical giant-cell areas	Well 10 years
18887	W	M	11	Clavicle and first rib	Tumor 9 months	0	Resection			Well 10 years
17708	C	F	49	Radius, left lower end	Pain 3 months	0	Resection	Bone shell intact	Fibrous reaction at capsule	Dead of other causes
16720	W	F		Radius, left lower end	Trauma 4 years	1 year	Resection	Bone shell intact	Typical giant-cell areas	Well 5 years
16898	W	F	24	Tibia, upper end	Tumor 18 months	0	Curetting		Typical giant-cell areas	Well 5 years
16580 }	W	M		Radius, lower end		0	Resection			Well 10 years
14880	W	F	31	Tibia, left upper end	Pain 6 months	0	Curetting	Bone shell intact		Well 10 years
14808	W	F	19	Tibia, lower end	Trauma 2 years	0	Resection		Fibrous reaction at capsule	Well 10 years
14421 }	W	M	40	Femur, lower end	Trauma 5 years	0	Curetting	Bone shell intact		Well 10 years
13088	W	M	34	Femur, right lower end	Pain 15 months	0	Curetting		Typical giant-cell areas	Well 10 years
12927		M		Radius, right lower end		0	Resection	Bone shell intact		Well 10 years
12474	W	M	45	Ulna, right lower end	Trauma 8 months	0	Resection	Bone shell perforated	Typical giant-cell areas	Well more than 5 years
12276	W	M	22	Tibia, left upper end	Pain 1 year	0	Resection	Bone shell perforated	Typical giant-cell areas	Well more than 5 years
11848	W	F	21	Fibula, right upper end	Trauma 7 months	0	Resection	Bone shell perforated	Typical giant-cell areas	Well 10 years
11828	W	F	37	Femur, lower end	Pain 2 years	0	Amputation	Bone shell perforated	Typical giant-cell areas	Well 10 years
10974	W	F	29	Tibia, upper end	Pain 30 months	0	Resection	Bone shell intact	Typical giant-cell areas	Well 10 years
9073	W	M	24	Ulna	Tumor 20 months	0	Resection		Typical giant-cell areas	Dead of other causes
8690	W	F	73	Radius, right lower end	Trauma 5 years	0	Resection	Bone shell intact	Typical giant-cell areas	Well 10 years
8886	W	F	48	Femur, lower end	Pain 6 months	Yes	Amputation	Bone shell perforated	Typical giant-cell areas	Dead of other causes
7731	W	F		Femur, lower end		Yes	Amputation	Bone shell perforated	Fibrous reaction at capsule	Well 10 years
6124	W	M	22	Radius, lower end	Pain 20 months	0	Resection	Bone shell perforated	Typical giant-cell areas	Well 20 years
6042	W			Radius, lower end		0	Refused	Bone shell perforated		Well 10 years
5601	W	F	52	Radius, left lower end	Trauma ½ year	9 yrs	Amputation	Bone shell perforated		Well 10 years
4306	W	F	21	Femur, lower end	Tumor 3 years	Yes	Amputation	Bone shell intact	Typical giant-cell areas	Well 10 years
3623	W	M	24	Femur, left lower end	Trauma 6 months	Yes	Amputation	Bone shell perforated	Typical giant-cell areas	Well 10 years
2458	W	M	29	Femur, lower end	Trauma 1 year	0	Amputation		Typical giant-cell areas	Discharged well
2420	W	M	23	Radius, lower end	Tumor 7 months	0	Amputation	Bone shell perforated	Typical giant-cell areas	Well 20 years
1815	W	M	44	Radius, lower end	Pain 22 months	28 mos.	Amputation	Bone shell perforated	Typical giant-cell areas	Well 20 years
723	W	M	26	Radius, left lower end	Trauma 3 months	0	Amputation			Well 20 years
275	C	F	45	Ulna, left lower end	Tumor 1 year	0	Resection		Typical giant-cell areas	Well more than 10 years

The only discrepancy is apparently in regard to the six lesions of the upper jaw. In Table 33 however it is seen that all of these tumors found their way either into the antrum or into the orbital fossa. The ethmoid bone, which is entirely derived from cartilage, is in relation to both of these cavities, as is shown in Figure 224 formed from cartilage and related to the normal resorptive process of bone by osteoclasts which takes place in the histogenesis of these bones. The predominant location of the giant-cell tumor in the epiphysis of the long bones, it was seen favored this view. The fact that the membrane bones of the skull are seldom involved by

TABLE 31 RELATIONSHIPS OF CENTERS OF OSSIFICATION OF THE CHONDROCRANIUM

Chondrocranial Region	Centers of Ossification	Part of Adult Skull
Occipital	Basi-occipital	Basilar process of occipital bone
	Exoccipitals	Occipital condyles
	Supra-occipital	Squamous portion of occipital bone below the superior nuchal line
Sphenoid	Basisphenoid	Body of sphenoid bone
	Presphenoid	Body of sphenoid bone
	Lingulae	
	Alae magnae	Greater part of alae magnae
	Alae parvae	Alae parvae
Periotic capsule	Petrous primordium	Petrous portion of temporal bone; Mastoid portion of temporal bone
	Nasal septum (mesethmoid)	Lamina perpendicularis; Crista galli; Nasal septum (cartilage)
Ethmoid	Paranasals (ectethmoids)	Lateral masses of ethmoid bone; Superior conchae; Middle conchae
	Cribriform plates	Cribriform plates
	Inferior conchae	Inferior conchae
	Sphenoidal conchae	Sphenoidal conchae

From Jordan and Kindred A Textbook of Embryology New York, Appleton 1926.

Interestingly enough, the illustration from Nelaton's work on giant-cell tumors published in 1860 shows a lesion of the upper jaw and the picture demonstrates clearly the relation of the tumor to the ethmoid bone and the inferior nasal concha. We have reproduced this illustration (Fig 226)

Unfortunately little regard has been paid in either the literature or clinic to the exact location of giant-cell tumors in the head. The available cases studied by us support the belief that the origin of the pathologic process is at the site of bone either bone cysts or simple giant-cell tumors confirms it.

SUBPERIOSTEAL GIANT-CELL TUMORS

Beside the giant-cell tumors of the skull, another group of lesions contributes to the interpretation of the pathologic nature of giant-cell tumor. This group is the subperiosteal giant-cell tumor which occurs in the shaft of the long bones and which presents unusual features that bear on the etiology of these lesions.

The subperiosteal giant-cell tumor com

Fig. 222. (After Toldt) The areas in black show the portions of the adult skull formed from cartilage (see Table 31)

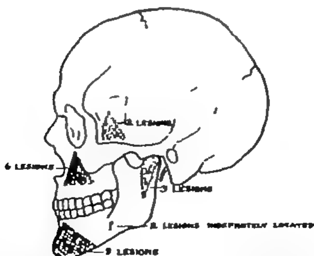


Fig. 223. Diagram illustrating the location of twenty-two giant-cell tumors of the skull. Compare with Figure 222. See also Tables 32 and 33.



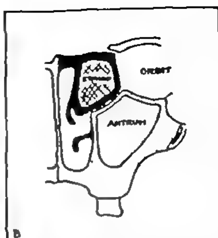


FIG. 224. (From Lothrop Ann Surg 38 233) (A) horizontal section above the level of the ostium maxillare. Within the figure (A) indicates the antrum with arrows indicating the position of the ostium maxillare and lying in the infundibulum, (U) uncinate process; the cavity just external to the letter is the infundibulum (a) (a) anterior ethmoid cells; (p) posterior ethmoid cells (s) septum nasi (O) orbital fossa (m.t) middle turbinates. The posterior half of each turbinate is horizontal, the anterior half is vertical, and in each instance the turbinate contains a cell (c) The dark space external to these turbinates is the middle meatus, and the long, dark area internal to the turbinates divided by the septum is the general cavity of the nasal fossa. The anatomic specimen shows the ethmoid bone which is formed from cartilage outlined in black and demonstrates the relation of this bone to the antrum and orbit. (B) (after Frazer: The Anatomy of the Human Skeleton, p 245) a diagram illustrating the position of the labyrinth of the ethmoid in relation to the orbit and antrum.

TABLE 32 GIANT-CELL TUMORS OF THE LOWER JAW

Path. No.	Dat	Race, Sex, Age			Location	Symptoms	Operation	Microscopic Appearance	Results of Treatment
43063	9/ 9/37	W	M	12	Mandible 1 canine	Tumor 1 year	Curetting	Typical giant-cell areas	Discharged well
36780	6/ 9/25	W	F	12	Mandible symphysis	Tumor 6 weeks	Curetting	Typical giant-cell areas	Well 14 years
36182	1/ 7/25	W			Mandible, ramus	Tumor	Resection	Typical giant-cell areas	Discharged well
36170	12/ 9/34	W	F	32	Mandible symphysis	Tumor 1 year	Curetting	Spindle-cell variant	Well 14 years
33246	4/10/34	W	M	16	Mandible, symphysis	Loose teeth	Curetting	Spindle-cell variant	Well 14 years
33091	8/18/33	W	F	23	Mandible, ramus	Tumor 3 years	Curetting	Spindle-cell variant	Recurred
29405	3/23/33	W	F	42	Mandible, symphysis	Tumor 10 months	Curetting	Spindle-cell variant	Discharged well
28297	6/21/31	W	M	6	Mandible, ramus	Tumor 6 months	Curetting	Spindle-cell variant	Discharged well
27281	10/31/30	W	F	20	Mandible	Tumor 5 months	Curetting	Spindle-cell variant	Well 1 year
27018	11/ 6/30	W	F	41	Mandible, symphysis	Tumor 3 months	Curetting	Spindle-cell variant	Well 6 years
141784	1/ 6/14	W	M	11	Mandible	Tumor	Curetting	Spindle-cell variant	Well 9 years
7614	10/ 0/06	W	M	10	Mandible symphysis	Tumor 2 months	Resection	Spindle-cell variant	Well 15 years
8227	1903	W	F	13	Mandible symphysis	Tumor	Resection	Spindle-cell variant	Well 17 years
3034	4/14/00	W	F	21	Mandible, symphysis	Tumor 10 months	Resection with glands	Spindle-cell variant	Well 21 years

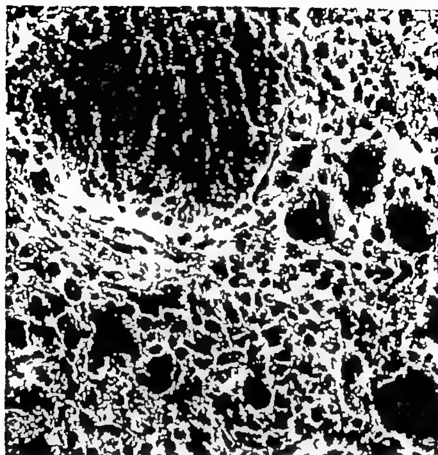


Fig. 225 (No 37914) A giant-cell tumor arising from the body of the sphenoid and presenting in the temporal fossa. Attention is directed to the relation of the giant cells to the newly formed blood cavity

Table 33 Giant-Cell Tumors of the Skull and Upper Jaw

Path N	Date	Race, Sex, Age			Location	Symptoms	Operation	Microscopic Appearance	Result of Treat[ment]
37914	2/ 1/23	W	F	[illegible]	Body of sphenoid	Pain 3 years	Excision	Typical giant-cell	Hemiph[illegible] years [illegible]
166304	6/ 0/03	W	F	14	Temporal fossa	Pain 18 months	Excision	None	Well 20
43109	2/21/28	W	31	0	Antrum, right	Tumor 6 months	Curetting	Spindle-cell variant	Dischar[illegible] well
37230	11/ 2/25	[illegible]	F	31	Antrum, left	Tumor 7 months	Exploration	Giant-cell tumor	Well 3 [illegible]
37106	9/22/25	W	F	13	Antrum, right	Tumor 2 months	Curetting	Spindle-cell variant	Well 8 y[illegible]
[illegible]	7/20/07	W	F	18	Antrum and orbit	Tumor	Partial curetting	Spindle-cell variant	Well 13 [illegible]
[illegible]	8/ 0/21	W	F	25	Antrum	Tumor 7 months	Curetting	Spindle-cell variant	Drainage sinus
[illegible]	8/21/11	W	F	?	Antrum, left	Tumor 3 weeks	Resection	Spindle-cell variant	Well 3 y[illegible]

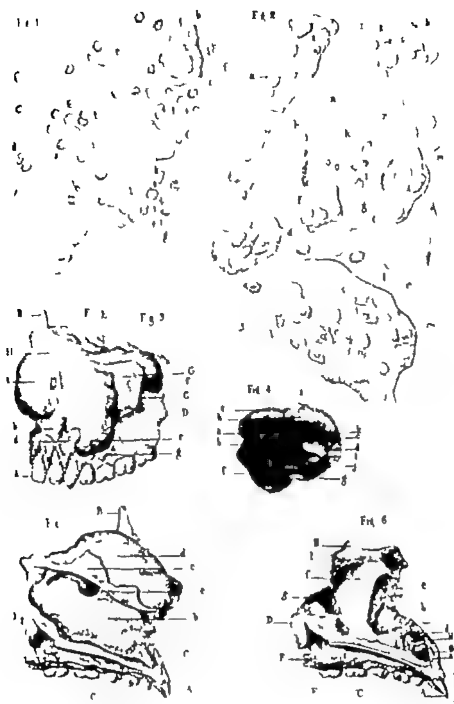


FIG. 228. (From Nélaton Tumeurs bénignes des os.) Illustrations of a benign giant-cell tumor arising in the ethmoid bone and presenting through the antrum into the maxilla. The resection of the jaw shows nicely the location of the tumor in the turbinates, which are derived from cartilage. (The capital letters of the alphabet were used by Nélaton to refer to normal structures, the smaller letters to the neoplastic features. Their keys have been omitted because of their irrelevancy here.)

prises a group which has been but recently recognized. Only four such cases are in this collection, and lesions of a similar nature are rarely reported in the literature. There is one excellent report by Cone who described it as an ossifying hematoma.



FIG. 227 (No 38372) Anterior and lateral roentgen views of subperiosteal osteoclasia occurring in the shaft of the ulna. The lesion is eight weeks old.

TABLE 34 SUBPERIOSTEAL OSTEOCLASIA

Path No.	Race, Sex, Age			Site	Duration	Treatment	Microscopic Appearance
37442	W	M	17	Femur cortical	6 weeks	Curettage	Giant-cell areas, osteitis fibrosa
38372	W	F	21	Ulna subperiosteal	8 weeks	Excision	Giant-cell areas, osteitis fibrosa
39293	W	F	58	Humerus subperiosteal	2 weeks	Curettage	Giant-cell areas, osteitis fibrosa
40124	W	F	16	Humerus cortical	8 weeks	Excision	Giant-cell areas, osteitis fibrosa

All lesions were observed since January 1926.

Cone, S.: Ossifying hematoma, J Bone & Joint Surg. 10: 474, 1928.

In this contribution the author who has long devoted himself to the study of pathologic changes in bone, observed that "osteitis fibrosa, hemorrhagic osteomyelitis and giant-cell tumor of bone have their representations in the microscopic pathology of this ossifying hematoma."

The data for the four cases comprising

this series are summarized in Table 34 In addition to the unusual location of the lesions beneath the periosteum of the shaft, the striking features brought out



FIG. 228. (No. 39293) Subperiosteal osteoclasia of two weeks duration. The photomicrograph shows the giant cells in relation to a newly formed blood cavity Young fibrous tissue is attempting to repair the lesions. Microscopically the tissue represents a borderline between giant-cell tumor and osteitis fibrosa.

are (1) the short duration of the symptoms (from two to eight weeks) (2) that trauma had usually occurred and (3) that all cases have been recorded since January 1926

The diagnosis of subperiosteal giant-cell tumor is dependent on an early roentgen examination of the patient following trauma. In the roentgenogram the periosteum is raised by a tumor casting little or no shadow and resembling a subperiosteal hematoma or hemangioma (Fig. 227) At the operation an extremely thin capsule or shell of bone described by the operators as a blue dome presents itself and when incised, a cavity containing blood is found. Tissue removed from this cavity and examined under the microscope shows giant

cells intermingled with ossifying fibrous tissue. In every case there was uncertainty whether the condition should be termed a cyst or a giant-cell tumor (Fig. 228)

In these cases it appears that trauma and hemorrhage followed by separation of the periosteum (with a subperiosteal osteogenic layer of tissue) are the initial pathologic events. In the cortex beneath the hemorrhage, a *disturbance in the periosteal* blood supply must occur and in the perios teum above, a healing reaction is stimu lated. In the group of lesions under dis- cussion the proliferation of osteoclasts arising as a result of injury is rapidly re gressive. The healing power of the under lying cortical bone and the overlying periosteum is evidently sufficient to over come any abnormal activity of the osteo- clasts. For this reason the duration of symptoms is short, and unless the patient comes under observation soon after injury and a roentgen examination is made the lesions disappear entirely or in unusual cases persist as an ossifying periosteitis.

Our interest is in the relation of hemor rhage, following trauma to giant-cell prolif eration. Evidently hemorrhage and a dis turbance of the normal blood supply of bone act as a stimulus to the proliferation of osteoclasts and may in some cases lead to an abnormal osteoclasia or giant-cell tumor This conclusion indicates that in the study of the blood supply of the region of the epiphysis and of factors that may dis *turb its normal functioning is to be found an* explanation of the origin of giant-cell tumor

ETIOLOGY OF GIANT-CELL TUMOR

It is much easier to discuss tumors in terms of etiology than to determine their be- ginning and subsequent histologic changes. For this reason, the literature abounds with references to the etiologic factors of trauma and hemorrhage in the production of giant cell tumor and bone cysts. Konjetzny* Lubarsch* and Pommer† are among t of the German school that have attem to connect the development of bone with medullary hemorrhage following ma. We are in accord with these au in placing trauma in a primary positi the production of these lesions. An att will be made, on the grounds of the en ologic observations pointed out earli *show just how trauma acts in producin* bone cyst and the giant-cell tumor

Relation of Osteoclasia to the Inte tion of the Periosteal Blood Supply In embryo permanent compact bone is down by the perichondrium or subpe teally and, as we have seen, this co bone takes a prominent part in the he reaction of fibro-ostosis after injury nourishment, this bone is partly depen on the periosteal blood supply In yo adults, this subperiosteal region contain extremely vascular and active tissue, new bone formation proceeds here m rapidly than elsewhere. On the other h the more primitive cancellous bone in medulla of the shaft which undergoes sorption and reconstruction by osteocl activity to form the medullary cavit nourished by vessels of the medulla, origin of which is from the nutrient ar The cancellous bone of the epiphys supplied from vessels which anastom around the joint, the diaphyseal, the m physeal and the epiphyseal, but as poi out by Poland‡ and shown in injected sp mens (Fig 229) by Lexer§ these ve pursue a periosteal and transcortical ro

The significance of this vascular arra ment in the origin of osteoclasia has b implied in the discussion of subperios

Konjetzny C. E. Die sogenannte "lokalisierte Osteitis Fibrosa," Arch. f klin. Chir 121 567 1922.

Lubarsch: Die Bedeutung des Traumas Entstehung und Wachstum krankhafter Gewa Med. Klin. 41 1615 1912.

† Pommer C.: Zur Kenntnis der progres Hematom und Phlegmasieveränderungen (H Haberers) Arch. f Orthop. u. Unfall.-Chir 1 vol. 17

‡ Poland, J: Traumatic Separation of the physes, London, 1898.

§ Lexer E.. Die Entstehung entzündli Knochenherde Arch. f klin. Chir 71 1 1903.

ant-cell tumor The evidence in that group lesions points to a vascular disturbance llowing trauma as a primary factor in the evelopment of giant-cell tumor

A significant observation in regard to the te of early lesions of progressive osteo-lasia must now be recalled. Early giant-cell tumors in the epiphysis (with a history of trauma from four to six months previously) practically always have an asymmetrical and subcortical location In other words, the giant-cell tumor and also the early bone cyst, arise at a point just beneath the traumatized area of the cortex. This is illustrated in the case shown in Figure 230. Here the lesion is near the surface of the bone in one of the condyles of the femur There was a *definite history* of trauma four and two months previously

Because of the prominence of the club-shaped epiphyseal region the cortical edge receives the brunt of the trauma in this locality Trauma acts on the cortex in relation to its periosteum avulsing the latter and interrupting the blood supply of the cortical bone. Normal vascular channels are thus supplanted by a subperiosteal hematoma. Interruption of the periosteal blood supply renders inactive the cortical bone on this side of the epiphyseal end, and its normal healing powers are suspended. The medullary circulation in the *region* of the epiphysis must take on an increased activity and by establishing new channels must work *its* way around the injured area to *undertake the work of repair*

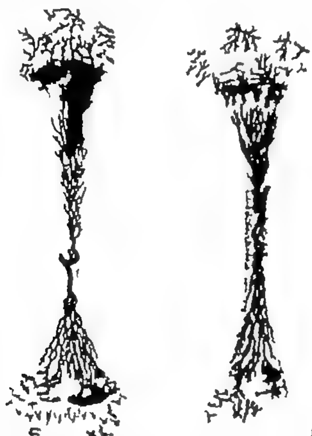


FIG. 229 (After Lexer Arch. f klin. Chir 71 1 1903) Injected specimens showing the epiphyseal blood supply in the long bones. The femur and tibia are represented.

This increased function of the medullary blood supply during the interruption of the

periosteal circulation can take place only after osteoclasts have opened up the chan nels in bone for the budding capillaries (for this we have seen is the normal order in histogenesis)

But this increased osteoclastic activity occurs where osteoclasts are already unus

In the metaphysis, the cortical bone, which is thick and vascular is apparently capable after a time of checking the osteoclasts. In the epiphysis, however bone destruction seems to proceed at a faster rate. The result is an arrested lesion or bone cyst in the metaphysis, and a progressive or un-



FIG. 230 (No. 20115) Giant-cell tumor with symptoms of two months duration in the epiphysis of the femur Attention is directed to the subcortical location of the lesion and the staining of the surrounding tissue by old blood. The specimen illustrates the typical site of origin of the giant-cell tumor

ually active in absorbing bone, and at the time when unnourished cortical bone is undergoing necrosis. An imbalance is thus created between bone destruction by osteoclasts and new bone formation that would normally proceed from the reactive cortex were its circulation intact. The defensive reaction of cortical bone, therefore, is sus pended while bone destruction by osteoclasts is at its height. This imbalance results in hyperplasia of the osteoclasts and produces a tissue characteristic of giant-cell tumor and the early phase of osteitis fibrosa or bone cysts.

checked lesion in the epiphysis. Even in the epiphysis, however the balance is probably restored in most cases. After tumor formation it can be restored if surgical intervention occurs before the bone shell is too extensively destroyed. If the osteoclastic tissue is removed by the curet and cautery and the walls crushed, healing will occur in most cases.

This osteoclastic activity to be of clinical significance must be engrafted upon a nor mal histogenic process. It must be super imposed upon osteoclastic resorption of calcified cartilage in the metaphysis in

young patients to cause a bone cyst and upon a similar process in the epiphysis in adults to produce a giant-cell tumor That additional metabolic factors may enter into the production of this imbalance is shown giant-cell areas and osteitis fibrosa-like tissue may be formed in the bone in animals fed with an excess of this substance.

Moreover repeated determinations of calcium and phosphorus in the blood serum



FIG. 231 (General pathology No. 58) A healing fracture in a rib of a normal dog Seven giant cells to the low power field are busy reforming the medullary cavity after callus formation. This illustrates the phase of osteoclastic proliferation in the normal healing process.

by the analysis of multiple giant-cell tumor and bone cysts presented elsewhere, and the studies on the serum calcium and phosphorus in parathyroid disturbances. The work of Jaffe has shown that increase in parathyroid hormone alone does not produce true tumors of this type although of patients with solitary giant-cell tumor or solitary bone cysts have failed to reveal abnormalities which would indicate hyperparathyroidism.

However giant-cell tumors may occasionally occur in the latter third of pregnancy We have seen several cases in the

long bones, and epulis of the alveolar margin developing during pregnancy is a well recognized clinical variety of giant-cell tumor Hamilton (personal communication) has demonstrated that the parathormone output is increased during pregnancy In several instances of giant-cell tumor occurring in patients between 39 and 60 years of age, the long bones in the unaffected extremity showed delayed union of the epiphysis. These findings suggest a possible disturbance in bone metabolism as a factor in the development of solitary giant-cell tumor

TABLE 35. SUMMARY OF TREATMENT IN TWO HUNDRED AND NINETY FOUR CASES OF GIANT-CELL TUMOR

Primary amputations	42 cases
Primary resections	34 cases
Curetting only	117 cases
Repeated curetting for recurrence	16 cases
Curetting plus amputation for recurrence	7 cases
Curetting plus resection for recurrence	10 cases
Curetting plus amputation for infection	3 cases
Resection plus amputation	2 cases
Exploration only	15 cases
Operation refused	9 cases
Roentgen therapy only	17 cases
No treatment recorded	22 cases
Total number of cases	294 cases
Total curettings	151 cases
Recurrent cases	37 cases
"Metastatic" cases not included in above	10 cases

THE TREATMENT OF GIANT-CELL TUMOR

Since the contributions of Bloodgood to the American literature of giant-cell tumor in 1910 and 1912,* the treatment has been increasingly conservative Amputation, then resection and then curettement have been the treatments of choice and now roentgen therapy alone is being advocated by some. The 294 followed cases forming the basis of the present study indicate this evolution in treatment, these cases recording the various forms of therapy practiced since 1898 (Table 35)

Primary Treatment Among the primary forms of treatment are listed amputation, resection, curettage, exploration and roentgen therapy only Of these various forms, curettement has been used most frequently Excluding the alleged metastatic group, and a few isolated giant-cell tumors of the skull and vertebrae (dangerous because of location) mortality either from treatment or from the tumor itself has been exceedingly rare—less than 1 per cent.

Amputation was the primary operation in 41 cases, and although one third of these cases were explored before amputation, and 20 had shown perforation of the bone shell prior to operation, there were no recurrences, no operative deaths and no patient died of tumor In slightly more than half of these cases the patients have remained well from 10 to 30 years and over but in spite of these uniformly good results, the sacrifice of the limb at a primary operation is rarely justified. Hardly ever is the lesion so advanced that the function of the limb is beyond restoration and even when pathologic fracture has occurred, it will heal with appropriate treatment. Particularly in the upper extremity the conservation of the limb or even one of its minor members should be attempted.

Resection was performed as the initial procedure in 34 cases. There were no deaths from either the operation or the tumor and if we except an excision of a tumor in the lower jaw recorded as resection and a

* Bloodgood, J C. The conservative treatment of giant-cell sarcoma, Ann. Surg. 56 210, 1912.

similar case in the radius, there was not a single recurrence. In 5 cases a portion of the bony shell was destroyed before operation in 3 pathologic fracture had occurred, and in 3 other cases, there had been a previous exploration Here again the mode of treatment was usually needlessly radical, and in 5 cases involving the tibia and 2 involving the femur in view of the functional results, curettage followed by cauterization would have been preferable. Preliminary roentgen therapy was not resorted to in a single instance in this group and in many the age of the patient and the extent of preservation of the bone shell favored treatment by curettage. Resection is permissible in advanced cases or in cases of elderly persons or with involvement of the fibula, radius or ulna, although in 11 cases in the ulna, in which the patients were treated by curettement, there was not a single recurrence.

In 166 cases primary curettage was the mode of treatment. The tumor in 31 of these cases recurred. One patient died of a tumor in the vertebrae, and another grew progressively worse after partial curettement of a giant-cell growth in the sphenoid bone, but after three operations is living and well 17 years later Seven patients became secondarily infected after the first or second curettement, necessitating amputation in three instances. Several of these infections followed radium implantation into the wound, a postoperative procedure which has proved ill advised in this group of tumors. Although it cannot be determined from the records in exactly how many instances thermal or chemical cauterization followed curettement, it can be safely stated from this study that recurrence was more frequent in the group in which no cauterization was employed. In view of this, and in consideration of the fact that the patient in 16 of the 31 recurrent cases were cured by a second or even third curettement, it may be stated that curettage properly performed* in carefully selected cases is unquestionably the treatment of choice.



Fig. 232. (No. 28091) Gross specimen of a giant-cell tumor amputated after two unsuccessful curettings. Note the destruction of cortical bone at one side of the tumor

Primary roentgen treatment without operation was employed in ten cases—all have been followed and are living. In five of these cases no benefit was obtained and surgery was subsequently employed. This therapy has proved successful in certain cases (Her

* The method advocated by Bloodgood consists of thorough curettage followed by cauterization with pure phenol subsequently neutralized by 95 per cent alcohol. A 50 per cent zinc chloride solution is finally applied. The electric cautery or soldering iron may be substituted for chemical cauterization. (Bloodgood, J C.: Ann. Surg. 69 345, 1919)

endeen)* reported in the literature (Fig. 217) The dosages, however must not be of full strength, lesions in the long bones and in adults under 50 respond more favorably and months are required to prove the effectiveness of the irradiation. When postoperative roentgen treatments have been given in certain instances, they have not prevented recurrence and would seem to be of no particular benefit. As Bloodgood has pointed out, roentgen therapy when compared to proper curettement, is more uncertain, often more prolonged, and does not offer the benefits of microscopic diagnosis in doubtful cases. Its use, however is indicated in lesions of the skull and vertebra when recurrence following surgery may prove fatal.

Ten patients refused operative treatment, and of these, eight have been followed, two are dead (one of hemorrhage) four are living over five years and two are well less than five years. One case after 20 years developed osteogenic sarcoma at the tumor site. Here there is a considerable risk of either crippling or death, and prompt treatment in view of the good results obtained in the majority of cases would have offered much to these misguided patients had they availed themselves of surgical advice.



FIG. 233 Photomicrograph made from section taken from the specimen shown in Figure 219 This giant-cell tumor has not altered its typical structure despite the two previous operations.

Secondary Treatment When curettage or excision has been followed by recurrence, the problem of the secondary treatment of giant-cell tumor arises. Experience shows that little can be expected from roentgeno therapy and more undesirable results may follow radium implantation into the wound. Prolonged irradiation has been followed by the development of osteogenic sarcoma in two of our cases. It has also been

* Herendeen, R. E.: Giant-cell tumors of bone, Am. J Surg. 8 122, 1930

reported by others, and therefore prolonged irradiation is to be avoided. If sections or tissue are available from the original operation they should be submitted to a competent pathologist for confirmation of the diagnosis. If not, the recurrent tumor should be reoperated on when there is an opportunity for one familiar with the microscopic appearances of this group of lesions to pass on the frozen sections. In any event, an attempt should be made to recheck the benign character of the growth. If the recurrence is benign, further curettement may be tried if the lesion is in the femur or tibia, and if the age of the patient and the degree of preservation of the bone warrant it. In the fibula, radius ulna or humerus, resection is advised.

Should the lesion be sarcoma, amputation is indicated, since one five-year cure in this series was obtained under such conditions. The crux of the matter of course, lies in an accurate pathologic diagnosis.

SUMMARY

In adults benign giant-cell tumor an epiphyseal lesion may invade and destroy the cancellous structure of the long bones. This lesion is most frequent in the lower end of the femur upper end of the tibia and lower end of the radius and gives rise to a more acute clinical picture than does the bone cyst, the symptoms averaging 14 months. The usual sequence of events is trauma, pain, tumor and pathologic fracture. In the roentgenograms the giant cell tumor shows a central defect situated asymmetrically in an epiphysis within a bone shell which is usually perforated. The lesion is progressive, and unless surgical intervention is attempted, or proper roentgen treatment is instituted, arrest cannot be hoped for Histogenetically the tumor is related to the resorption of calcified cartilage by giant cells which occurs as a step in normal bone growth in the region of the epiphysis until late in life, and under the microscope this is shown by many large multinucleated giant cells predominating in a vascular stroma of small plump spindle cells.

The occurrence of giant-cell tumors in the skull follows the distribution of the cartilaginous centers of ossification supporting the view that these tumors are related to the normal process of ossification via cartilage. In the skull the age incidence is a decade younger than in the long bones.

In the etiology of giant-cell tumor trauma with interruption of the periosteal blood supply with inhibition of the normal reactive processes in cortical bone may play a role in the production of these new growths.

The treatment of giant-cell tumor depends upon whether the lesion is seen as a primary condition or whether it is recurrent. In a primary case, not too far advanced, curettement followed by cauterization is advocated, particularly for the lower femur and upper tibia. In advanced cases in the fibula, ulna or radius, resection is preferred. In early cases and in lesions of the skull and vertebrae deep roentgenotherapy may be given a trial Once the giant-cell tumor has recurred, resection is the treatment of choice, except in those bones in which resection is equivalent to amputation of the limb. Here further curettement, cauterization and filling the cavity with bone chips should be tried. Repeated irradiation is dangerous and may be followed by osteogenic sarcoma.

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14

Microscopic Variants and Recurrent Cases of Giant-Cell Tumor

Many recent contributions to the literature have sought to emphasize the relationship of giant-cell tumor to forms of osteogenic sarcoma and to correlate variations in the clinical or microscopic picture with varying degrees of malignancy Since from the standpoint of prognosis and treatment, it is of great practical importance to be familiar with these variant forms of giant-cell tumor and conversant with their differentiation from osteogenic sarcoma these atypical groups are considered in detail in the present chapter

THE SPINDLE-CELL VARIANT OF THE GIANT-CELL TUMOR

Encapsulation of the giant-cell tumor is accomplished by a healing reaction at its margin resembling histologically the shell of a benign bone cyst. This healing reaction of fibro-ostosis predominates in sections taken from the margins of giant-cell tumors. A single section under the microscope will often show a giant-cell area, a border of spindle cells, a further outlying zone of ossifying fibrous tissue and finally a region of reacting cortical bone demonstrating clearly the nature of the healing reaction and the attempt by nature to lay down a defensive wall (Fig 234)

In 37 among 294 cases showing this spindle-cell variation under the microscope (Tables 36 and 37) the fibroid change was fairly uniform throughout the tumor This group of cases is of unusual interest because, histologically this type of lesion has not infrequently been regarded as a more malignant type of giant-cell tumor (Ewing*) whereas in the present study they were found to resemble in their behavior benign bone cysts Clinically these tumors were all located in bones other than the long pipe bones, 8 were in the vertebrae and 29 were in the small bones of the hands and feet or in the flat bones The interpretation placed on these lesions was that they represented giant-cell tumors in which the healing reaction was unusually prominent. The clinical follow-up on this group of cases confirmed this. None of these patients died of tumor if we may except one who proved inoperable when a laminectomy was attempted on a tumor near the sacral region. With this exception, the other patients are well without signs of recurrence. On the other hand, in the typical giant-cell tumor recurrences follow similar treatment in over 20 per cent of the cases.

This group of lesions raises the question as to why the giant-cell tumor of the epiphysis fails to heal and is a progressive lesion, while a similar tumor in the small or flat bones progresses partially toward healing, and the bone cyst arising in the metaphysis of the long bones presents a predominantly healing reaction. The explanation lies in the differences in the anatomic structure of the bones involved. The epiphysis is the site for giant-cell tumor the metaphysis for the bone cyst and the small

* Ewing, J: Neoplastic Diseases, ed. 3, Philadelphia, Saunders, 1918, p 314, Fig. 110.

TABLE 30. SPINDLE-CELL VARIANTS OF GIANT-CELL TUMORS IN THE SMALL BONES

Path. N	Race, Sex, Age	Location	Symptoms	Roentgen Findings	Treatment	Microscopic Appearance	Results of Treatment
28514	W M 60	Hand, phalanx	Pain 8 years	Bone shell intact	Roentgen	Spindle-cell stroma	Discharged well
39174	W F 30	Metatarsal, tarsal	Tumor 1 year	Bone shell intact	Curetting	Spindle-cell stroma	Well less than 5 years
37170	W F 46	Hand, phalanx	Trauma 6 months	Bone shell perforated	Amputation	Spindle-cell stroma	Dead 19 years
31316	W F 16	Metacarpal, carpal	Tumor 10 weeks	Bone shell intact	Excision	Spindle-cell stroma	Well less than 5 years
32209	W F 17	Metacarpal, carpal	Tumor 6 months	Bone shell perforated	Amputation	Spindle-cell stroma	Well 26 years
29103	W F 25	Metatarsal, tarsal	Tumor 13 years	Multiple encapsulated	Resection	Spindle-cell stroma	Well more than 5 years
24692	W M 34	Metacarpal, carpal	Tumor 10 months	Bone shell perforated	Amputation	Spindle-cell stroma	Well less than 5 years
17646	M	Foot, phalanx	No note	No note	Amputation	Spindle-cell stroma	Discharged well
17436	W F 41	Oscalcis	Trauma 3 years	Multiple, encapsulated	Curettage	Spindle-cell stroma	Well 10 years
17007	26	Astragalus	Tumor	No note	Resection	No note	Well 5 years
16725	W M 30	Astragalus	Pain	Bone shell intact	Curettage	Spindle-cell stroma	Well 10 years
241321	W M 33	Oscalcis	Trauma 9 months	Bone shell perforated	Curettage	Spindle-cell stroma	Well 10 years
23373	W F 23	Vertebra, 5th lumbar	Trauma 6 months	Multiple, encapsulated	Curettage	Spindle-cell stroma	Discharged well
28330	W F	Vertebra, 3d lumbar	Tumor	No note	Exploration	Spindle-cell stroma	Unimproved
201913*	W M 16	Vertebra, 10th dorsal	Trauma 3 months	Bone shell intact	Resection	Spindle-cell stroma	Well more than 5 years
29716*	W M 14	Vertebra, 4, 5 lumbar	Trauma 7 weeks	No note	Curettage	No note	Well more than 5 years
29482	W F 8	Vertebra, 2, 3 dorsal	Paraplegia 1 month	Bone shell intact	Curettage	Spindle-cell stroma	Well more than 5 years
16707	W F 11	Vertebra, 5th lumbar	Pain 4 months	No note	Curettage	Spindle-cell stroma	Well when discharged
12033		Vertebra				Spindle-cell stroma	Well less than 5 years
10984	W M 24	Sacrum, 5th lumbar	Paraplegia	No note	Exploration	Spindle-cell stroma	Died of tumor

In Table 35 are shown lesions of a similar nature, with a greater healing reaction

TABLE 37 GIANT-CELL VARIANT OF OSTEITIS FIBROSA IN THE SMALL AND FLAT BONES

Path. N	Race, Sex, Age	Lesion	Symptoms	Treatment	Microscopic Appearance	Results of Treatment
[illegible]14	W M [illegible]	Metacarpal	Tumor 4 months	Curettage	Osteitis fibrosa with giant-cell areas	Well 12 years
26182	W M 11	Metatarsal	Tumor 6 months	Resection	Spindle-cell variant predominated by giant cells	Discharged well
25104*	W M	Vertebra, 4th dorsal	Paralysis	Laminectomy	Spindle-cell variant predominated by giant cells	Well 1 year
31657	W M 51	Metacarpal	Trauma 10 months	Amputation	Spindle-cell variant predominated by giant cells	Well 6 years
29990	W F 31	Patella	Trauma 13 months	Curettage	Spindle-cell variant predominated by giant cells	Well 6 years
27625*		Metacarpal	Tumor	Excision	Cyst with giant cells	Well 7 years
27302	W F 4	Metacarpal	Tumor	Excision	Cyst with giant cells infected	Well 3 years
29043	W F 22	Hand, phalanx	Tumor 6 months	Amputation	Spindle-cell variant with cysts and giant cells	Well 8 years. Lost
17049*	W M 20	Astragalus	Trauma 1 year	Curettage	Cyst with giant cells	Well 6 years
13597*	W M	Hand phalanx	Tumor	Amputation	Cyst with giant cells	Discharged well
10834	W M 19	Metatarsal	Trauma 3 years	Amputation	Spindle-cell variant predominated by giant cells	Discharged well
26484*	W F	Pelvis	Tumor 3 years	Exploration	Osteitis fibrosa with giant cells	Well 1 year
34166	W M 41	Pelvis	Trauma 15 months	Curettage	Giant-cells against cartilage	Well 5 years
29674	W F 28	Rib, 10th	Pain 6 years	Resection	Spindle-cell variant predominated by giant cells	Well 4 years
26641	W M 23	Pelvis	Trauma 2 years	Curettage	Osteitis fibrosa with giant-cell areas	Well 8 years
31660	W M 73	Clavicle	Fracture 50 years	Excision	Osteitis fibrosa with giant-cell areas	Well 9 years
12278	W F	Pelvis	Pain 1 month	Excision	Osteitis fibrosa with giant-cell areas	Well 18 years

* Sections were not seen by the authors.

or flat bones for the spindle-cell variant of giant-cell tumor The epiphysis in which the typical giant-cell tumor occurs lacks the defensive mechanism represented by the thick cortex of the metaphysis and the diaphysis and also, as Poland has pointed out, lacks the rich and vascular osteogenic layer found in the periosteum of the shaft. Hence, the giant-cell tumor progresses in the epiphysis, whereas the same bone-destructive lesion in the metaphysis is reacted to effectively by the cortical bone to form a walled-off cyst (Fig. 209) On the other hand, in the small bones, spacial limitations bring the tumor almost immediately into relation with cortical bone on all sides and an early defensive reaction is set up which microscopically exhibits itself as a fibrous proliferation resulting in the so-called spindle-cell variant (Fig 236) This tendency toward repair however although invoked early is not so marked as in the shaft of the long bones in which the cortex is thicker and more active

That lesions with characteristics of the giant-cell tumor in small bones are often diagnosed as bone cysts demonstrates their healing tendencies.



FIG. 234. (No 17706) Section taken from the periosteal margin of a giant-cell tumor New bone formation preceded by a layer of fibrous tissue is attempting to wall off the tumor

Dean Lewis* in his paper on giant-cell tumor of the vertebrae emphasizes this point. In this contribution Lewis reviews 17 cases including one of his own, pointing out that recovery after partial removal or exploration only has been noted in 13 of the 17 cases, ossification occurring frequently In his series, the lesion in 2 cases was located in the transverse processes of the lumbar vertebrae, 2 in the lamina of dorsal vertebrae and the majority of the re-

Poland, J Traumatic Separation of the Epiphyses, London. Smith, Elder 1898.

Lewis Dean: Primary giant-cell tumors of the vertebrae, J.A.M.A. 83 1224, 1924.

mainder (as far as can be determined from the case reports) in the lateral portions of the body next to the lamina. As will be seen from Figure 238, the site of these tumors is in the region of compact bone and the early defensive reaction of fibro-ostosis accounts for the healing emphasized by Lewis.

RECURRENT GIANT-CELL TUMOR AND MALIGNANT VARIANTS

Recently Goforth, Jaffe, Stewart and others* attempted to grade the microscopic picture to show the gradual transition of benign giant-cell tumor to osteogenic sarcoma. Microscopic studies of giant-cell tumors in this laboratory have been carried out in an effort to confirm or possibly to elucidate this alleged malignant transformation of giant-cell tumors. While granting the possibility of sarcoma arising at the site of a preceding benign giant-cell tumor a transitional stage has not been observed.

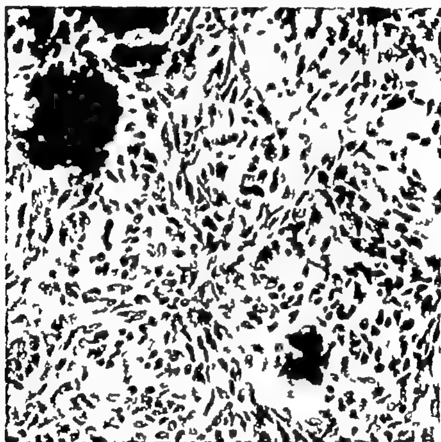


FIG. 235. (No. 11855) A giant-cell tumor showing spindle-cell variation near the tumor margin. Spindle cells are infiltrating about the large giant cells.

Sections from these cases (Fig 239) show spindle-cell variation Perforation and extension into neighboring bones occur more frequently in giant-cell tumors of the spindle-cell group (12 of 17 in Lewis series) but this is only because they occur so frequently in small or flat bones in which the cortex is always thin and other bones are in close approximation (Fig 240) Extension is not due to increased virulence of the tumor as some pathologists claim who consider the spindle-cell variant of the giant cell tumor a malignant form of this lesion.

In approaching this problem microscopic analysis alone is insufficient, and therefore the cases with clinical recurrence have been

* Goforth, J L.: Giant-cell tumor of bone. Arch. Surg. 13 846, 1926.

added in the study of the microscopic variants.

CLINICAL FEATURES LEADING TO RECURRENCE

In this group of lesions the original tumor was always characterized by a microscopic ascribed either to a poor selection of the type of treatment for the individual case or to an incomplete operation. The failure of these tumors to follow the usual course and heal after a primary curettage can be usually explained by the clinical features of the case.

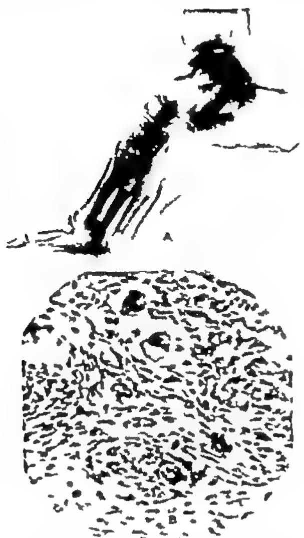


FIG. 230 (No 17436) Giant-cell tumor in the os calcis. The roentgenograms, (A) shows mottling and bone destruction The shell of bone is intact. The microscopic structure (B) shows a spindle-cell variant of the giant-cell tumor

structure typical of the benign giant-cell tumor and the failure of these lesions therefore to heal after a primary curetting cannot be explained on a histologic basis. A study of the 26 cases in this group (Table 38) reveals that the recurrences are to be

In deciding upon the treatment to be instituted, age must be considered. In the group of patients with giant-cell tumors cured by curettage 21 per cent were over 30 and 41 per cent were between 20 and 30 years. In the recurrent groups of giant





FIG 237 No 26953) The roentgenogram, (A) shows a giant-cell tumor of the terminal phalanx of the midfinger There is involvement of both shaft and epiphysis in this small bone and the tumor has perforated at the distal end. The photomicrograph, (B) shows a giant-cell tumor in the phalanx of a toe. Portions of trabeculae of cancellous bone are undergoing absorption, while the proliferation of fibroblasts in other areas shows a healing reaction.

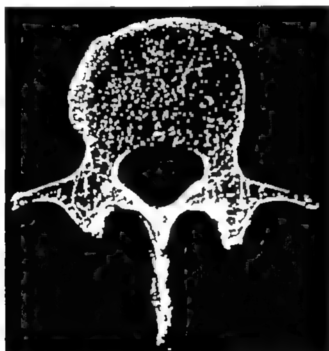


FIG. 238. (After Triepel-Breslau Anat. Hefte 25 209) Cross-section of a lumbar vertebra showing the relation of cancellous to compact bone. As is explained in the text, the most frequent site of giant-cell tumors is in the region of the laminae in the body in the transverse process or in the lamina itself This brings the tumor into contact with compact bone at an early stage.

cell tumor 42 per cent were over 30 years of age and only 16 per cent were in their twenties. There is, therefore, a difference between the ages in the recurrent and in the nonrecurrent groups with a definite tendency for the giant-cell tumor to recur more frequently in persons over 30 years. This is to be explained by the fact that cortical bone declines in its power to heal and ossify after the age of 21, and as we have pointed out previously this cortical bone is a primary factor in the healing reaction about a giant-cell tumor

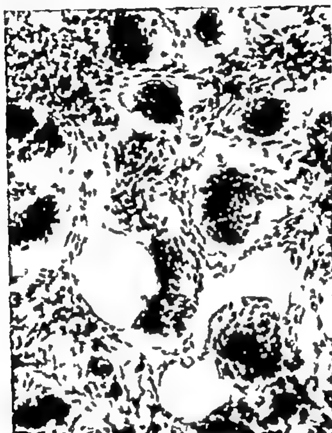


FIG. 239 (No. 38530) Giant-cell tumor of a vertebra. The giant cells are embedded in a stroma in which there are many spindle cells

The location of the tumor is also of some significance as regards recurrence. While recurrent giant-cell tumors occur in most of the sites of origin, the lower end of the radius appears to be a favorite location for the return of the lesion after curetting (Fig. 242) The upper part of the tibia shows relatively few recurrences (8 per cent) and the lower part of the femur a moderate number (39 per cent) while in a series of 16 curettings in the lower part of the radius, the tumor recurred in 50 per cent. The explanation of these frequent recurrences in the radius lies in the destruction of the bony shell, which usually has progressed to a further degree in this non weight-bearing bone than in the bones of the leg before the patient experiences severe symptoms. The average duration of symptoms is 20 months in the radius compared with 14 months for the giant-cell tumor in other long bones.

Both age and the sites of recurrences emphasize the influence of cortical bone in the healing of giant-cell tumor after curettement. The most valuable asset in the cure of a giant-cell tumor is the preserved shell of cortical bone with an intact and sufficient

blood supply This is indicated by spontaneous healing of giant-cell tumors to produce a bone cyst in the metaphysis and shaft of the long bones in which there is a substantial layer of cortical bone with a highly vascular subperiosteal mantle.

Roentgenograms and gross specimens emphasize the fact that the giant-cell tumor most frequently recurs because curettement rather than resection has been undertaken in a tumor that has destroyed too much of the bony shell before the surgical intervention (Figs. 243 and 244) Such destruction is also the major cause of failure in treatment by deep roentgenotherapy The perforation of a giant-cell tumor into the soft parts is to be feared because of the cortic destruction antecedent to the perforat and because of extension and the danger of incompletely removing the soft part tumor (Table 38)

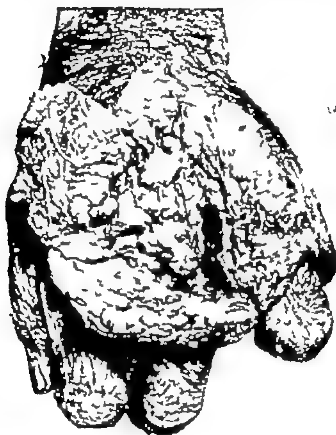


FIG 240 (No 24682) Gross specimen showing the evolvement of the third and fourth metacarpals by giant-cell tumor There is extension of the bone-destructive process to several bones.

In seven of the cases in this series the recurrence of the tumor could be ascribed to partial curettement. Usually the failure to remove all of the tumor was due to an erroneous diagnosis which led to simple aspirations or to incomplete excision, in the belief that a suppurative lesion existed. In one case the operation was incomplete because of hemorrhage.

In curetting, care should be taken to remove as much of the cancellous bone involved as possible, and at the same time to conserve cortical bone with intact blood

v With removal of too much cortical repeated operations are often neces

sary and each time more and more of the cortical bone is sacrificed, until cure by curettage becomes impossible

That no giant-cell tumor has recurred after primary radical resection or amputation emphasizes that the kind of treatment and not the histology of the tumor is the primary factor in recurrence. As Bloodgood has pointed out, the typical giant-cell tumor is benign and conservative treatment by curettement and cauterization is the operation of choice. This is particularly true when resection of a weight bearing bone would cause marked deformity or disability But in elderly patients and in cases in which much of the bone shell is destroyed and in sites such as the fibula, ulna radius and humerus when resection with transplantation of bone will restore function, discrimination between curettement and resection should be carefully made Resection of the upper tibia with transplantation of a graft from the opposite fibula has resulted in a useful limb twice in the present series. Before attempting such radical resection however a second curetting is worthy

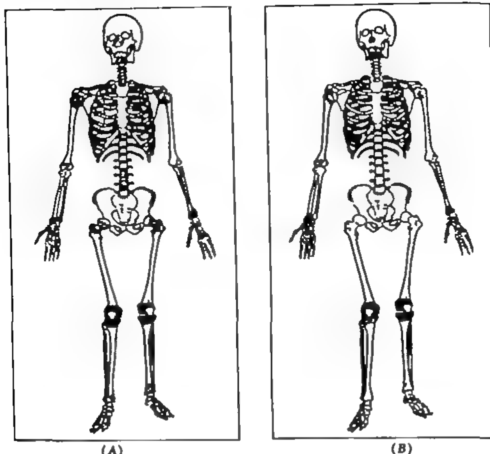


FIG. 241 (A) Chart showing the skeletal sites involved by 222 giant cell tumors. The solid black area indicates the most frequent sites, the checked areas, the common sites, and the diagonal lines, the occasional sites. Other sites are exceedingly rare. Note that the epiphyseal regions are most often affected. (B) Chart showing the skeletal sites involved by 21 recurrent giant-cell tumors. The solid black area indicates the most frequent sites, the checked areas the common sites; and the diagonal lines the occasional sites.

Bloodgood, J C. The conservative treatment of giant cell sarcoma, Ann. Surg. 56 210 191_

TABLE 38. CASES WITH CLINICAL FEATURES LEADING TO RECURRENCE

Symptoms	Roentgen Findings	Treatment	Microscopic Appearance	Cause of Recurrence	Results of Treatment
		1st curetting 2d curetting, 1927	2d oper typical	Shell destroyed	Recurred twice
	Bone shell intact	1st curetting, 1925 postoperative radiation	1st oper typical	Age over 30	Living 9 years. Lost
Pain, tumor	Shell destroyed	1st curetting, Feb., 1927 cautery resection, April, 1928	1st oper typical	Shell destroyed	Living 11 years
Trauma, pain, tumor		1st curetting, 1912 2d curetting, Dec. 1925	1st oper typical 2d oper typical	Age over 30	Living 15 years
Trauma, pain	Bone shell destroyed	1st curetting, June, 1926 resection, Sept., 1927	1st oper typical 2d oper fibrous variant	Age over 30 Shell destroyed	Well 2 years
[illegible]mor	Bone shell destroyed	1st resection, May, 1924 radiation, Sept., 1924 cauterization, Jan., 1925	1st oper typical 2d oper fibrous variant	Bone shell destroyed	Well 2 years
[illegible]se teeth, tumor	Bone shell perforated	1st curetting, April, 1920 2d curetting, April, 1922 with cauterization	2d oper fibrous variant	Bone shell perforated	Living 3 years
Trauma, pain, tumor	Bone shell perforated	1st resection, May 1921 2d resection, Jan 1923	Bone healing Few giant cells	Bone shell perforated	Well 5 years
Trauma, pain, tumor		1st curetting, Feb., 1917 2d curetting, Oct 1917 3d curetting, July 1919 with radium	1st oper typical	Poor curetting (?)	Well 9 years
Tumor	Bone shell perforated	1st curetting, March, 1912 resection, June, 1914	2d oper fibrous variant	Bone shell perforated	Well 14 years
Weakness, trauma, pain	Bone shell perforated	1st curetting, July 1921 radium implantation resection, Jan., 1921	1st oper typical	Bone shell perforated	Well 7 years
[illegible]uma, tumor	Bone shell perforated	1st curetting, Nov 1919 postoperative radiation 2d curetting, Feb 1921 with cautery and radium	1st oper typical, foam cells present	Bone shell perforated	Lost
Trauma, pain, tumor	Bone shell intact	Aspirated, April, 1919 1st curetting, May 1919 with cautery 2d curetting, June, 1919 with cautery	Fibrous variant, second and third operation	Treated as osteomyelitis	Well 8 years

27[illegible]		Femur lower		Pain, tumor		Partial curetting, 1919 2d curetting, Aug 1919 [illegible] cautery		Treated as osteomyelitis	Well [illegible] years Lost
[illegible]	W F 2[illegible]	Tibia, upper	13	Trauma, pain, tumor	Bone shell perforated	1st curetting, May 1918 [illegible] tomes 2d curetting, Jan 1920 amputation, Dec 192[illegible]	2d oper fibrous variant	Bone shell perforated cortical bone sacrificed [illegible] t operation	Well 9 years Lost
2[illegible]0[illegible]1	N M 27	Femur lower	2	Pain, tumor	Bone shell perforated	Amputation, April, 1919 curettage July 1919 amputation May 1920	2d oper typical	Treated as arthritis	Well 9 years, Lost
[illegible]	W F 2[illegible]	Radius, lower	6	Pain, tumor	Bone shell perforated	1st curetting, July 1917 [illegible] cautery 2d curetting, July 1918 [illegible] cautery	1st oper typical	Bone shell perforated	Well 3 years
24[illegible]21	W M 2[illegible]	Os calcis	9	Trauma, pain, tumor	Bone shell destroyed	1st curetting, July 1911 infection 2d curetting, Nov 1913 with cauterization	1st oper typical	Bone shell destroyed	Well 15 years
14044	W F 2[illegible]	Radius, lower		Tumor		1st curetting, 1909 amputation, 1910	1st oper typical	N data	Well 6 years
1[illegible]	W F 2[illegible]	Fibula, upper	15	Trauma, pain, tumor	Bone shell perforated	1st curetting, May 1911 resection, 1916	1st oper typical	Bone shell perforated	Well 12 years
10[illegible]	W F 2[illegible]	Radius, lower	5	Trauma, pain, tumor	Bone shell perforated	Partial curetting, 1905 2d curetting, Sept., 1906	1 t oper typical	Incomplet curetting because of hemorrhage	Well 20 years
[illegible]	W M 2[illegible]	Femur lower		Pain, tumor	Bone shell perforated	1st curetting, March, 1900 resection, July 1909	1st oper typical	Bone shell perforated	Well 11 years
[illegible]	W M [illegible]	Radius, lower	20	Trauma, pain, tumor	Bone shell perforated	Partial curetting, 1906 2d and 3d curetting, 1906 resection, Aug 1907	3d oper fibrous variant	Treated as tuberculosis	Well [illegible] years
7440	W M 2[illegible]	Femur lower	6	Trauma, pain, tumor	Bone shell perforated	1st curetting, Jan., 1906 amputation, Sept 1906	1st oper typical	Bone shell perforated	Well 22 years
45[illegible]	W F 19	Femur upper		Tumor fracture		Exploration, tomes, 1899 1st curetting, 1901 2d curetting, 1902	1st oper typical	Exploration without treatment	Well 26 years
14[illegible]	W M 2[illegible]	Tibia, upper	14	Trauma, pain, tumor		Partial excision, 19[illegible] 1st curetting, Aug 1906	Sections lost	Incomplete operation	Well 7 years

of a trial. The possible benefits resulting from collapsing the cavity by crushing* or by filling it with bone chips must be considered when curettement is employed.

MALIGNANT VARIANTS AND DIFFERENTIAL MICROSCOPIC DIAGNOSIS IN GIANT-CELL TUMOR

In this group seven lesions showed under the microscope characteristics resembling arising in the differential microscopic diagnosis. All the important variations in the histologic picture of this tumor are seen, such as changes due to necrosis from poor fixation, alterations dependent on recurrence and infection, modifications caused by partial healing with fibrosis, changes brought about by irradiation or by infiltration of adjacent tissues, as well as the actual presence of osteogenic sarcoma in the sec-



FIG. 242. (No 37708) Roentgenogram of a giant-cell tumor of the lower part of the radius showing extensive destruction of the bone shell *which led to a recurrence of the tumor after* curetting

osteogenic sarcoma (Table 39) Practically all of these cases were submitted to various pathologists for diagnosis, and in most instances there was a striking lack of agreement among those most competent to judge. Although ultimate clinical results favor the conclusion that the tumors were benign (no deaths are recorded in the follow-ups) still in three instances (No. 29327 No. 39404, No. 26792) the microscopic structure is indistinguishable from certain varieties of osteogenic sarcoma.

This small group of cases selected from among 294 cases of giant-cell t r on strates practically all the poin n

tions. An analysis, therefore, of this small group of so-called malignant variants of giant-cell tumor serves admirably as a study in the differential diagnosis of this growth, as far as microscopic changes are concerned. It serves to emphasize the importance of a familiarity with changes produced in the histology of giant-cell tumor by previous operations, irradiation, partial healing, in fection, invasion of soft parts and poor fix ation.

Clinical Fe The clinical features of these "m ariants are given in Table 39 It n that five of seven cases recurr tial curetting or ex cision, and croscopic variations are generall with a se nd or third operat ervenin on.

Henderson, M S: Giant cell upper end of the femur Minnesota 1928.

In other words, instead of the so-called ma lignant microscopic structure being the cause of the recurrence, the reverse is true—the infection of the recurrent tumor is usu ally the cause for the microscopic change Death has not been recorded in any of the seven cases. Two patients alive, five and six years respectively after treatment, were subjected to resection or amputation, and



FIG. 243 (No. 32924) Roent genogram of a giant-cell tumor in the lower end of the fibula, similar to the case shown in Figure 242. Advanced destruction of the shell of cortical bone was responsible in all probability for the recurrence after curettement in this case

such treatment, which may result in cure in genuine sarcoma, must be considered in evaluating the character and clinical course of the growth.

Microscopic Analysis. In the cases listed in Table 39 the condition in all seven cases was diagnosed osteogenic sarcoma by the majority of the pathologists passing on the sections. In the case in which sections from the first operation were seen (No. 32924) poor fixation resulting in necrosis was responsible for the inability to distinguish between sarcoma and a variant of giant-cell tumor In the other four cases, owing to lack of knowledge of the history or to actual

errors in the clinical or clerical recor pathologist making the diagnosis was formed that he was looking at a re lesion and not the original tumor case (No 30170) a marked healing r



FIG. 244 (No. 32924) Gr specimen of the tumor shown Figure 243 The shell is perforat and infection followed.

caused a resemblance to fibrosarco in the other three cases infection ac for the marked pyknosis and clouc ing of the nuclei, interpreted as a fe osteogenic sarcoma. Unfamiliarity changes in giant-cell tumor prod partial healing after a primary ope by infection was therefore the m most of the diagnostic errors in thi

In the cases in which infection curred, the pyknosis and cloudy resulting simulated malignancy larly when examination was mad high magnification (Fig 246) magnification is perhaps more re

TABLE 30 MALIGNANT VARIANTS OF GIANT-CELL TUMOR

P N	Race, Sex and Age	Location	Duration, mo	Symptoms	Roentgen Findings	Treatment	Microscopic Appearance	Cause of Microscopic Change	Results of Treatment
30434	W F [illegible]	Scapula	6	Pain, tumor	Bone shell intact	Curetted 1927	Calcified areas	Sarcoma	Well 1 years
	23	Lower jaw	12	Tumor	Bone shell intact	Partial curetting, 1923 by dentist 2d curetting, Oct 1924	2d oper young fibrous tissue with new bone	Healing after 1st operation	Well 3 years
	9	Fibula, lower	3	Trauma, pain, tumor	Bone shell perforated	1st curetting, April, 1923 2d curetting, May 1923 with cauterization resection, Aug. 1923	1st oper necrotic tissue 2d oper infected tissue	Necrosis and infection	Well 5 years
	W M 19	Femur lower	4	Trauma, tumor	Bone shell intact	Exploration, Oct. 1920 followed by infection 1st curetting, Nov 1921 with cauterization amputation, 1922	2d oper infected tissue 3d oper malignant variant Section indistinguishable from osteogenic sarcoma	Infection	Well 18 years
			16	Trauma, pain	Shell thin intact	Curetting Cauterizing Radium Toxins	Calcified areas	Sarcoma	Well 18 years
			24	Trauma, pain, tumor	Bone shell intact	Partial curetting, 1916 2d curetting, July 1916 3d curetting, July 1920 3d curetting, July 1920	3d oper infectious changes	Infection	Well 19 years
	N M 40	Vertebrae	18	Pain, tumor		Partial excision, 1919 Further excision, 1919 Further excision, 1920	3d oper infectious changes	Infection	Well 3 years

arriving at a correct diagnosis. When thus examined there was more loose fibrous tissue, a less cellular stroma and more nu clear débris than is seen in sarcoma under lower magnification. The giant cells present were larger and more numerous and con- tained over 15 nuclei to the cell, which is not typical of osteogenic sarcoma. Analysis under high-power magnification of the large vesicular nuclei in these infected cases showed that often they were composed of several smaller nuclei which were undergoing clumping and losing the finer markings of their former structure, with the gradual formation of an amorphous mass.

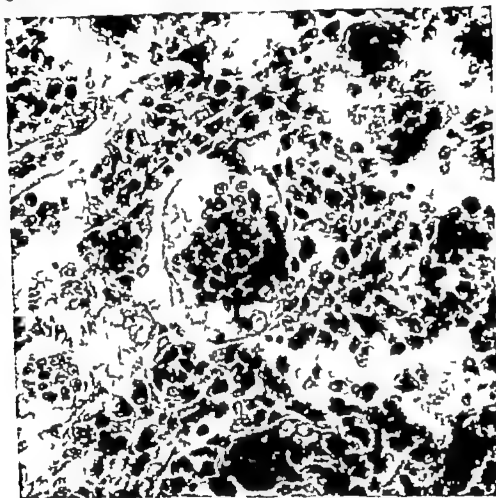


Fig. 245 (No 56324) Photomicrograph of a typical giant-cell tumor occurring in the upper tibia. The tumor was treated by curettement in September 1932. Sarcoma occurred at the tumor site in December 1935 (see Fig 247)

In any case, therefore in which a bone tumor containing numerous large giant cells averaging over 15 nuclei per cell is seen with round-cell and polymorphonuclear in filtration and many areas of hemorrhage sur rounded by young, loose fibrous tissue the pathologist should be on his guard against making a diagnosis of sarcoma and wary lest the apparent malignancy of the nuclear material may be, in reality pyknosis and cloudy swelling dependent on infection and degeneration.

In summarizing this study of the "malig nant variants" of giant-cell tumor two questions of long standing may be answered. *First, what is* the relation of the microscopic picture of a "malignant variant" to recur

rence after curetting, and second, what is the relation of the "malignant variant" of giant-cell tumor to osteogenic sarcoma.

In answer to the first, it may be said that "malignant" modification in the microscopic structure of a giant-cell tumor is *usually* *the result* and not the *cause of recurrence*. When the "malignant variant" structure is primary and recurrence results, metastasis is apt to follow showing that in a few instances a genuine sarcoma has been masquerading under the false diagnosis of giant-cell tumor

In answer to the second question, of the relation of such sarcomas to giant-cell tumors, we may say that the giant-cell phase of osteogenic sarcoma is usually a secondary process in which giant cells are invading malignant areas of chondroblastic or osteolytic sarcoma in response to the abortive calcified or osseous material. In benign giant-cell tumor the giant-cell areas are primary and are secondarily invaded by bone of the benign reactive type. From the point of view therefore, of differential diagnosis, the question to be decided is the type of new bone or ossifying tissue present.

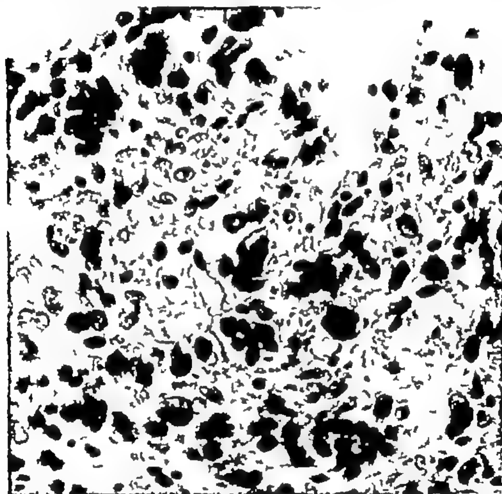


Fig. 246 The malignant variant of the giant-cell tumor Four large and several small giant cells are seen in the field. Among the small round cells of the stroma are larger cells with more cytoplasm and vesicular nuclei simulating sarcoma.

THE METASTATIC GROUPS

Recently there has been an attempt to show that the typical giant-cell tumor called benign may occasionally metastasize and produce death. Stone and Ewing, Co-

forth, and Finch and Gleave are among those who have published reports of unusual giant-cell tumors, apparently typical in structure, but peculiar in behavior Goforth stated that "an occasional case is met with, which although locally malignant, and in a few instances actually metastasizing, apparently does belong to the giant-cell tumor

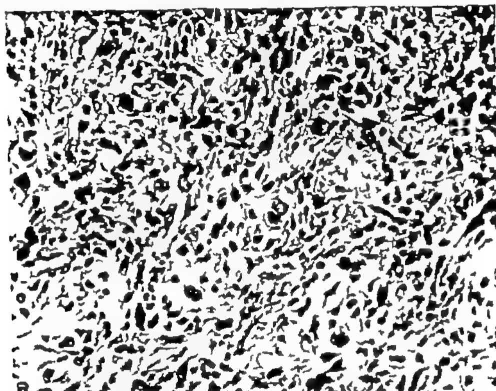


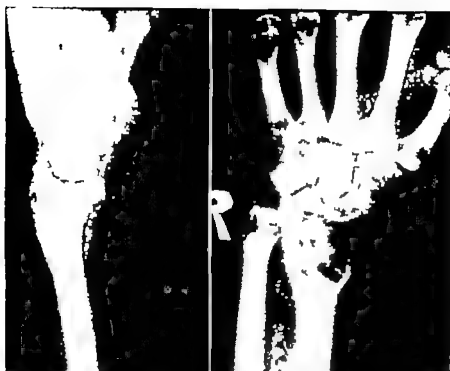
FIG. 247 (No 56324) Photomicrograph of an osteolytic osteogenic sarcoma occurring at the site of a previous benign giant-cell tumor (see Fig 245) The sarcoma surrounded old areas of calcification containing a few giant cells.

group." Similar statements are frequently found in the literature with illustrative case reports, and it would seem that there is a tendency for the pendulum to swing away from the more fundamental contributions of Nélaton Paget and Bloodgood on the benign nature of the giant-cell tumor

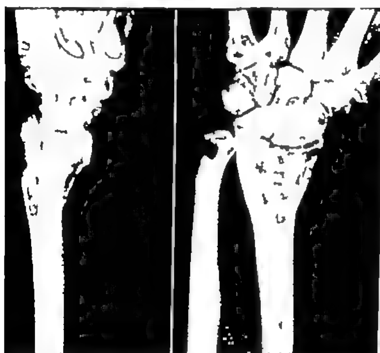
Eight such cases from the literature and from the records of the surgical pathological laboratory of the Johns Hopkins Hospital have been studied. Sections of all of these cases are in the laboratory and are available for study The eight cases analyzed represent the unusual members of a much larger series from the clinics of New York Philadelphia, Chicago Baltimore, Canada and England—in all a series of well over 500 cases.

One important conclusion stands out in analysis of this material In no case has a nodule of typical giant-cell tumor ever been found in the lung, for wherever these metastatic nodules have been examined, they have shown the histology of osteogenic sarcoma.

On the whole, pathologists are agreed that regardless of their opinion as to the nature of the original growth, the actual metastasizing lesion is not giant-cell tumor but an osteogenic sarcoma. It may be taken as proved that a giant-cell tumor found to be typical by a competent pathologist is safely treated conservatively The question, therefore, is not whether a giant-cell



(A)



(B)

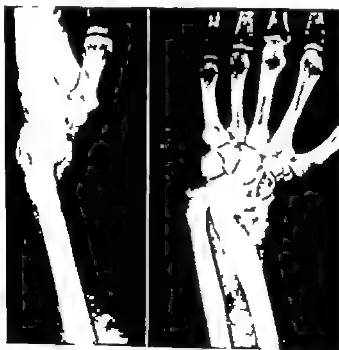
FIG. 248. Roentgenograms of a benign giant-cell tumor of the lower right radius which underwent malignant change ten years after curettage and postoperative irradiation. Amputation was performed for the malignant lesion and the patient is well four years later (A) Roentgenogram of original lesion, taken in 1932 before curettage. (B) Roentgenogram taken in 1933, showing partial healing

tumor will metastasize—it never does*—but whether these growths when they recur after improper treatment will undergo malignant change and give rise to osteogenic sarcoma. This question must be answered in the affirmative.

In an analysis of eight reported cases and two of our own selected as metastatic from among hundreds of typically benign giant-cell tumors, transformation of giant cell tumor into sarcoma has been proved, but in no case have typical secondary giant cell tumor nodules been found in the lungs. In half of the cases a diagnostic error was made, either in ascribing death from other causes to metastases, or in failing to recognize the histology of the original lesion as sarcoma. In the other four cases, material from the original lesion was not saved for confirmation of the diagnosis. In a few isolated instances, a benign giant-cell tumor when subjected to unsuccessful treatment and to trauma, may by its failure to heal provide a fertile site for the subsequent development of osteogenic sarcoma. The unhealed area of bone, and not the nature of the original lesion however is the important factor

The following case illustrates this point. The patient was a white male aged 45 who had roentgenograms taken of the upper left tibia following 10 months discomfort in the left knee joint. A typical giant-cell tumor which had perforated the cortex at one point was disclosed in the films. Curettement was performed in September 1932, and the tissue removed proved to be typical benign giant-cell tumor (Fig 245) In November postoperative irradiation was given. Between the end of 1932 and 1934,

* Two cases have been reported with thrombi of benign giant-cell tumor tissue in regional veins. (Brit. J Surg. 20: 269 1932, J.A.M.A. 93 1224, 1934.)



(C)

following curettement. (C) Roentgenogram taken in 1943, after repeated irradiation and recurrence. A biopsy of this lesion showed an osteogenic sarcoma. (Case of Dr Paul O'Donnell, Washington, D C.)

repeated films were made of the left tibia and showed a gradual healing process. In December 1935 tenderness and swelling reappeared at the tumor site. The films at this time showed the original area surrounded by a dense rim of new bone. Beyond this and invading the entire upper third of the tibia was a honeycombed region of rarefaction, with a faint overlying periosteal reaction

The tibia was explored in February 1936, three years and five months after the primary operation Typical osteolytic sarcoma was disclosed (Fig. 247) and the leg was amputated. In the gross specimen there were several areas of calcification and a few giant cells, but the greater part of the tumor tissue was fully developed osteogenic sarcoma. Within four months following amputation, metastases to the chest were visible in the roentgenogram. The patient died with extensive pulmonary metastases in August, 1936.

A similar case is pictured in Figure 248 A man of 50 complained of pain and discomfort in the right wrist for 10 months, in 1932. Roentgenograms disclosed a bone-destructive lesion in the lower radius. The lesion was explored and curetted and was microscopically a benign giant-cell tumor It healed partially in 1933 following postoperative irradiation. Several courses of irradiation were given over the next five years. In 1943, there was recurrent pain and tenderness and increasing deformity of the right wrist. The roentgenogram disclosed extensive destruction in the lower end of the radius, with a periosteal reaction. The lesion was biopsied and sections showed an osteogenic sarcoma. Amputation of the extremity above the wrist, was performed in 1944. The patient is living and well in 1949

Our experience with more than 200 giant cell tumors over the past 20 years justifies the following conclusion Great care must be taken to distinguish osteolytic osteogenic sarcoma, with giant cells, from benign giant cell tumor particularly when the lesion is at the upper tibia or lower femur and in a patient under 20 years. In the roentgenograms, the sarcoma will have melted the bony shell and provoked a periosteal reaction. Under the microscope, the stroma of such tumors will contain malignant fibroblasts.

If the lesion is a benign giant-cell tumor with clinical symptoms of 6 to 14 months duration, and the microscopic picture is typical it may be treated conservatively with curettage or resection according to location. Postoperative irradiation adds nothing to such treatment and is contraindicated because it may ultimately eventuate in malignant change.

When the lesion has persisted for more than 14 months, and symptoms date back over 10 years, spontaneous malignant change may have occurred and both benign giant-cell tumor and osteogenic sarcoma may be found in the same lesion in different areas This is a rare occurrence, and has been reported once in our series, and once in the literature.

SUMMARY

Atypical cases of giant-cell tumor include the spindle-cell variant, which is a healing form of giant-cell tumor found usually in small bones. Clinical recurrences due to faulty selection of the type of operation in the individual case or to insufficient treatment because of an erroneous diagnosis are also included. The so-called malignant variant of giant-cell tumor in which the microscopic picture, because of infection and necrosis, approaches that of osteogenic sarcoma, belongs in this group The so-called metastatic giant-cell tumors have been found upon analysis to include benign giant-cell tumors with death from other causes, forms of osteogenic sarcoma erroneously diagnosed as benign in the first instance and chronic benign lesions of obscure nature ultimately leading to malignant change. The truly metastatic group of giant-cell tumors comprises cases of recurrent giant cell tumor which after prolonged and inadequate treatment have furnished a nidus for the development of osteogenic

sarcoma Most of these cases have had repeated postoperative irradiation In the treatment of these atypical cases, the operative measures must depend upon a careful differential microscopic diagnosis.

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15

Extraskeletal Giant-Cell Tumors

GIANT-CELL EPULIS—ODONTOCLASTOMA

The term epulis (on the gums) has a purely regional significance. Angiomas, granulomas and hypertrophied epithelium as well as giant-cell tumors are often included in this group of lesions. The giant cell epulis is a tumor of the alveolar margins occurring most frequently near the canine or bicuspid teeth in children or young adults. The tumors are usually firm and redder than the surrounding mucous membrane and preceded by trauma or local irritation. Symptoms other than a localized swelling of from one to two centimeters in diameter are rare.

Varieties. Under the lower power of the microscope, the presence of stratified epithelium growing downward into the tumor from the mucous membranes of the gum must be relied on to differentiate many of these growths of the alveolar margin from the typical giant-cell tumor (Fig. 249) The giant cells are of the usual multinucleated type and differ from those in the giant-cell tumor of the long bones in no important detail. In the stroma of the epulis there is a tendency to fibrous modification or a leukocytic infiltration, but this is not essentially different from giant-cell tumors of bone.

In the so-called fibroid epulis, under the microscope, the tumor is practically always without giant cells. When these occur they are few and small (Fig 250) In some places the fibroblasts are transformed into osteoblasts which are laying down the intercellular substance of osteoid tissue resembling osteitis fibrosa. Organized hemorrhage is also present.

Microscopic analysis, therefore divides epulis into a giant-cell variety which is practically indistinguishable in its fundamental histology from giant-cell tumor and a fibrous variety which is the exact homologue of osteitis fibrosa. There are only minute variations, such as a slight modification in the morphology of the giant cell in the first class of epulides and the tendency of the second class to be solid rather than a thin walled cyst. The conclusion that we are dealing with the same type of pathologic process here as in the cyst and the giant-cell tumor in the long bones is unavoidable. However the epulis is found only along the alveolar borders of the upper and lower maxillae, which are membranous bones, and it is a periosteal rather than a medullary lesion.

These two facts constitute an apparent exception to the rule that giant-cell tumor and its healing phase, osteitis fibrosa, always occur in the medulla of intracartilaginous bone as a consequence of a dysfunction in the normal osteoclastic resorption of this type of bone. The belief that the giant-cell tumor is an exaggeration of such osteoclastic activity contests such an exception to the general rule and demands that epulis be brought into intimate relationship with a *normal osteoclastic hyperplasia.*

Origin. At the outset it is necessary to exclude from a diagnostic standpoint a large number of the cases usually classed as epulis. When this group is restricted on microscopic grounds to the lesions already described under the giant-cell and fibroid epulis, a clinical entity is obtained which is more readily analyzed.



FIG. 249 (Nos. 26824 and 36458) Epulis of the giant-cell type on the upper alveolar border (A) illustrates the gross and (B) the microscopic. The giant-cell areas are some distance from the mucous membrane and are shown in the lower right hand corner of (B)

Epulides of this restricted category have been shown beyond a doubt to be periosteal in origin. Bloodgood* has shown that the lesions arise from the alveolar dental periosteum. They may arise either under the mucous membrane of the gum immediately surrounding a tooth or from the interior of the socket itself Besides this close association with the periosteum of the teeth, they occur only at the alveolar borders of the maxilla in the regions extending from the first molar on the one side to the first molar on the opposite side. An epulis practically never occurs behind or in the

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of the last molar and rarely at the site of any of the permanent molars. This point was emphasized by Scudder* in a review of 178 cases compiled from various clinics. They are most frequent near the canine and bicuspid teeth. Clinically this relation to the teeth is further emphasized by the and increase in size are never rapid until the tumor has escaped the confines of the alveolar border and is proliferating over the margins of the gum. The patients are most often children or young adults.

It is a consideration of these clinical features of epulis that gives a clue to the path-



FIG. 250 (No 23768) Photomicrograph illustrating the fibroid type of epulis. Note the resemblance to osteitis fibrosa

symptoms of the patient, who gives a history of a carious tooth or some other dental irritation. The patient generally refers to the growth in its early stages as a gum boil, but the advanced stages may show a tremendous overgrowth of tissue protruding over the jaw and outside of the oral cavity The growth of the epulis is outward and practically never invades the bone but pushes upward through the gums in the crevices about the teeth or in a fossa where a tooth has been pulled. The overgrowth

ologic changes in this disease. First, they arise only about the periosteal borders of certain teeth. Second, they practically never occur at the site of the molar teeth. Third, they grow outwardly and proliferate only after escaping the alveolar border Fourth, they occur most frequently in children (not infants) and in young adults. The age incidence and the site of the lesion are invaluable in disclosing the nature of the pathologic The features of the age limits and th the epulis to occur about

lars appear but once and are perma f epulides can be related to the nor rocess of shedding the deciduous which begins at the age of 5 and ex to the thirteenth year the histogen this process should explain the nature epulis and correlate the pathologic s in this lesion with those in other ell tumors. This expectation is ful when a study is made of the embry of the teeth and the histologic process ich they are shed. Here the hyper of osteoclasts seen in giant-cell tu duplicated by an analogous process, ich there is a proliferation of odonto- that are instrumental in loosening issolving the roots of the deciduous

nore detail the histology is as follows eciduous teeth are anchored by a thin of dental cement which surrounds ots and are invested by a periosteal (or pericementum) which forms at he outward coat of the roots and the teum of the jaw uniting the one to the The pericementum stops at the neck tooth and forms an annular thicken- conjunction with the dense connec- issue of the gum that is known as the ar dental ligament. The cementum it membranous bone and differs in no tial from this type of bone found else- in the body When the child is about ge of five years, odontoclasts arising he pericementum or periosteum of the proliferate and absorb the cementum roots of the deciduous teeth and thus the way for the eruption of the perma teeth (Fig. 251)

out the roots of the deciduous teeth, fore, there is a periosteum which is ally endowed with the power of osteo- . This osteoclastic hyperplasia is a nor occurrence after the age of five and is e a provision for shedding the decidu eeth. The process is analogous to the clastic hyperplasia that occurs in the of the long bones and in the cartilagi bones of the skull. It is the natural method of the absorption of cartilaginous bone. The deciduous teeth, therefore, are in part like cartilaginous bone in that both are temporary bony structures and the pathologic process of giant-cell tumor arises in connection with either in one case giving origin to epulis and in the other to the typical giant-cell tumor of the long bones.

That there is a fibroid type of epulis just as there is osteitis fibrosa in relation to giant-cell tumor confirms this view The fibroid epulis is the evidence of the healing reaction of the periosteum about the lesion This healing reaction, like that elsewhere in the periosteum and subperiosteal layers of bone, is an efficient defense against osteoclasia or giant-cell tumor We have seen that it is capable of arresting a giant-cell tumor or bone cyst in the shaft of a bone At the epiphysis, however where periosteum and cortical bone are deficient, the giant-cell tumor is progressive and breaks through. In the same way in regard to epulis, the fibroid reaction (or as we choose to call it fibro-ostosis) is an efficient barrier to the tumor It practically never invades the body of the jaw unless there has been undue trauma or some other factor The ability of the epulis to progress and to proliferate over the gum, however is due to the fact that periosteum ceases at the surface of the tooth, and it is through this gap about the teeth that the epulis erupts.

There are few other places in the body to our knowledge, in which the periosteum is endowed normally with such osteoclasia as here at the alveolar border although it is true, as is demonstrated in the absorption of callus after fracture that all periosteum has some osteoclastic power The unique situation, therefore, of epulis is readily comprehended. These tumors are connected with the shedding of the deciduous teeth, and the age incidence of them is related to the eruption of the permanent teeth as is shown in Table 40

It will be seen that there is a latent period between the appearance of epulis and the shedding of the teeth. In other words, there

is a lapse of time between cause and effect, which may be attributed to the slow and benign course of these lesions. But the important point is that the epulis does not proliferation of the odontoclasts, and the process is best termed odontoclasia, which avoids the confusing miscellaneous group of conditions that for years have been care-



FIG. 251 (After Arey Am. J Anat. 26 315) Giant-cell osteoclasts about the roots of the deciduous teeth of young pigs. (ocl.) indicates giant-cell osteoclasts; mtx., matrix of teeth roots and (obl.) osteoblasts.

occur before the age of 5, and this is due to the fact that the permanent teeth do not begin to erupt until the age of 6 Instead of being an exception to the rule that giant cell tumor follows on a normal proliferation of osteoclasts, the epulis, therefore, presents valuable evidence in confirmation of this view These lesions are related to a normal lessly thrown together under the term of epulis.

Treatment The treatment of epulis should be conservative. Although these lesions may grow to large size, or recur after simple excision, they have never been known to undergo malignant change or to metastasize. The removal should always be guided

by microscopic examination of the tissue excised. In the giant-cell type of epulis, the complete excision should be made, extending into healthy mucous membrane: it is well to cauterize the remaining wound. Such complete extirpation need not involve the removal of one or more teeth. Successful treatment by irradiation has been reported, but if not carefully administered may lead to bone necrosis and radiation osteitis. Conservative surgery is preferable.

TABLE 40 AGE INCIDENCE OF EPULIS IN RELATION TO ERUPTION OF PERMANENT TEETH

Age of Eruption of Permanent Teeth*		Age Incidence of Epulis†	
First molars	6th year	5 to 10 years	6 cases
Two central incisors	7th year	10 to 20 years	17 cases
Two lateral incisors	8th year	20 to 30 years	7 cases
First premolars	9th year	30 to 43 years	9 cases
Second premolars	10th year		
Canines	11th and 12th year		39 cases
Second molars	12th and 13th year		
Third molars.	17th and 25th year		

* Gray's Anatomy ed. 21 1924, p. 1124.
† All patients were over 5½ years and under 43 years of age. No lesions occurred at the site of the third molar

XANTHOMA (SYNOVIOMA)

The view that the giant-cell tumor arises as an obnormal phase in the osteoclastic resorption of cartilaginous or temporary bone may be applied to the pathologic changes in the giant-cell tumors of the xanthoma group. These giant-cell xanthomas of the tendon sheath are also referred to as benign synoviomas.

Varieties. Since Lebert,* in 1845 introduced the term "xanthos" to denote a group of yellow fibrous tumors, a large and miscellaneous collection of entities has accumulated under that heading. A group of skin lesions under the names of xanthoma palpebrarum, xanthoma diabeticorum and xanthoma multiplex may be set aside here because giant cells are absent in and atypical of this series. While containing lipoid pigments, blood pigment is usually wanting in these lesions The xanthomatous tumors connected with the joints and tendons, however frequently contain typical giant cells and are related to the group of skin lesions mentioned only by their characteristic yellow color which has been shown definitely to be due to blood pigment or lipoids and hence nonspecific. Phagocytes engulfing these lipoids and containing cholesterol have been referred to in the literature as foam cells and occur just as indiscriminately in this series of tumors as does pigment, being less frequent but equally nonspecific. These foam cells also accompany at times, typical giant-cell areas, and the presence of these cells in otherwise typical giant-cell tumors of the long bones has led to the use of the term xanthosarcoma of bone by some authors.

Writers on the subject of xanthomatous tumors are agreed that this group comprises neither a clinical nor a pathologic entity But since the giant-cell areas have been viewed as nonspecific granulation tissue and both pigment and foam cells have been proved to be nonspecific, a criterion has been lacking for the analysis of this group.

From the practical standpoint, three separate types of tumors which may contain macrophages and giant cells occur in the tendon sheaths and about the joints. The most common is the benign synovioma, which is predominantly a fibroid tumor derived from the mesenchymal tissues of the

* Lebert Physiologie et pathologie, vol. 2, Paris D. Baillière, 1845 p. 120.

tendon sheaths. The second is the symptomatic xanthoma, composed of lipoid granulation tissue, with foam cells predominating. This is found in patients with diabetes, jaundice, familial cholesterolemia, forms of *nephritis* or *hypothyroidism*. The third is the true giant-cell tumor which may arise in the synovial membranes or in aberrant sesamoid bones. (See Chap. 24.)

Since the time of Chassaignac* (1852) and *Billroth*† (1868) clinical peculiarities in regard to giant-cell tumors of the tendon sheaths have repeatedly caused them to be placed in the xanthoma group. More recently Tourneux‡ (1913) Beekman§ (1915) Broders‖ (1917) Garrett¶ (1924) and Mason and Woolston** (1927) have emphasized the tendency for these tumors to occur on the hand about the fingers and on the foot and about the ankle. Although the exact limits of the group are pathologically ill defined, Mason and Woolston were able to collect 144 cases including 8 of their own, which could be placed in this class with reasonable assurance because of their characteristic location and peculiar histology. The clinical summary by these authors shows that the sexes are about equally affected, that adults of an age between 35 and 40 predominate. The size of these firm yellow tumors ranges between that of a pea and that of an egg. The course of the disease is benign but protracted (average duration four and one-fourth years). Trauma as an etiologic factor is noted in from 30 to 40 per cent of the cases.

We have restudied this group of tumors and have had the privilege of checking the studies made by Garrett in this laboratory in 1923, who reviewed 196 lesions of the joints, bursae, tendons and of the subcutaneous tissues. Our restudies with over

TABLE 41. GIANT-CELL TUMORS OF TENDON SHEATHS

Path. No.	Race, Sex, Age	Location	Trauma	Duration	Microscopic Appearance
42995	W M 38	Little finger, flexor surface		6 years	Typical giant-cell areas
41183	W F 60	Index finger			Typical giant-cell areas
41030	W M	Finger			Typical giant-cell areas
40638	W F	Ring finger, flexor surface		4 years	Typical giant-cell areas
39503	W F 16	Thumb, ulnar side			Typical giant-cell areas
38633	W F 13	Ring finger, flexor surface	Yes	13 months	Typical giant-cell areas
35890	W M 28	Index finger, extensor surface	Yes	5 years	Typical giant-cell areas
35023	W M 27	Middle finger			Typical giant-cell areas
34371	W M	Index finger, flexor surface		2 years	Typical giant-cell areas
32960		Finger			Typical giant-cell areas
32450	W M 23	Index finger, flexor surface	Yes	1 year	Typical giant-cell areas
31688	W M 7	Great toe, medial side		4 months	Bone and giant-cell areas
29643	W F 30	Index finger, flexor surface		3 years	Typical giant-cell areas
28997	W F 27	Middle finger, flexor surface		10 weeks	Typical giant-cell areas
28360	W M 50	Index finger, flexor surface, ring finger		1 year	Typical giant-cell areas
27150	W F 18	Ankle			Typical giant-cell areas
26128	W F 32	Middle finger, multiple	Yes	3 years	Typical giant-cell areas
21728	W M 24	Ring finger, flexor surface	Yes	6 years	Typical giant-cell areas
20814	W M 48	Foot, metatarsal		30 years	Cartilage and giant-cell areas
16030	W M	Hand			Typical giant-cell areas
15773	W F 58	Foot, instep, tarsal bones eroded		14 years	Typical giant-cell areas
15237	W M 50	Ankle	Yes	8 years	Typical giant-cell areas
14718	W F	Finger			Typical giant-cell areas
11004	W F 38	Index finger			Typical giant-cell areas
9137	W M 28	Foot			Typical giant-cell areas
2590	W M 30	Thumb, flexor surface	Yes	18 years	Typical giant-cell areas
1650	W M 46	Ankle, medial side		22 years	Typical giant-cell areas

* Chassaignac. Gaz. d. hôp. 1852, p. 185.

† *Billroth, cited by Beekman: Giant-cell tumors* of the tendon sheaths, Ann. Surg. 62: 739, 1915.

‡ Tourneux, J. P. Les sarcomes des gaines tendineuses, Rev. de chir. 47: 817, 1913.

§ Beekman, F. Giant-cell tumors of the tendon sheaths, Ann. Surg. 62: 738, 1915.

‖ Broders, A. C. Benign xanthic extraperiosteal tumor of the extremities containing foreign body giant cells, Ann. Surg. 70: 574, 1919.

¶ Garrett, C. A. Tumors of the xanthoma type, Arch. Surg. 8: 882, 1924.

** Mason, M. L., and Woolston, W. H. Isolated giant-cell xanthomatic tumors of the fingers, Arch. Surg. 15: 499, 1927.

100 additional cases in the same groups accumulated since that time permit a segregation of 27 lesions with a xanthic color containing fairly typical giant-cell areas. The group thus histologically restricted presents more forcibly certain clinical and pathologic peculiarities.

equally striking. Fibrosis of a marked degree akin to the spindle-cell variant of giant-cell tumor or to the fibroid type of epulis predominates in the stroma about the giant-cell areas. This fibrous tissue takes an unusually brilliant pink stain with hematoxylin and eosin and forms a peculiar lat-

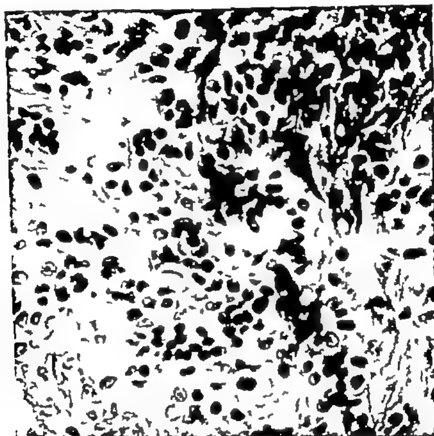


FIG. 252A. (No. 42995) High-power photomicrograph of a giant-cell xanthoma of the tendon sheaths. Note the network of intercellular substance, the giant cells and the numerous round cells. A few larger cells resembling cartilage cells are seen among the fibrous network.

As shown in Table 41, 18 of the 27 lesions were located on the fingers at the metacarpophalangeal or interphalangeal joints. Most of these were on the flexor surface. The remainder, with few exceptions, were elsewhere on the hand or about the foot and ankle. This predilection of the tumors for the tendons in special regions is of more than passing significance.

Not only are the localities peculiar but the histologic structure of these lesions is

tice work in special areas enclosing cells that resemble cartilage cells (Fig. 252). Giant cells of the usual epulis type, large and multinucleated, are numerous, and frequently average more than 30 to a low-powered field. They are embedded in the round-cell stroma typical of giant-cell tumor and conspicuously not the round-cell infiltration seen in granulation tissue. Occasionally the foam cell characteristic of other types of xanthoma is present, but this

type of cell has also been observed in 5 per cent of the giant-cell tumors occurring in the long bones.

Under the microscope, pigment is a conspicuous feature of most of these tumors. As Smith* showed by his studies in this laboratory this pigment is old blood pigment and gives the typical iron reaction.

Origin of Giant-Cell Tumors of the Tendon Sheaths. Fortunately there were available in the laboratory several giant-cell tumors of the patella. Seven such tumors of the patella recorded as variants of either the bone cyst or the giant-cell tumor have been reviewed by Cole,* and King and Towne† described a similar tumor of the patella. The

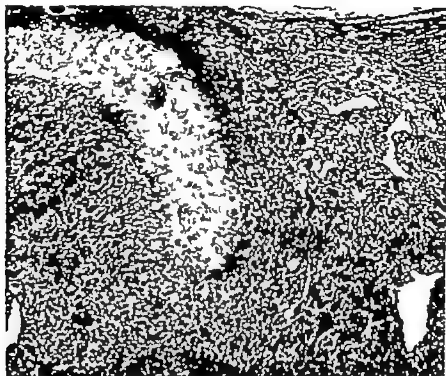


FIG. 252B Photomicrograph of giant-cell tumor of a sesamoid bone. Note the newly formed bone spicule at the margin adjacent to the tendon sheath.

Since we reject on histologic grounds the current granulation tissue theory of the origin of these lesions, it is necessary for us to demonstrate a connection between these tumors and some bony or cartilaginous structure. Heretofore attempts to establish such a relationship have failed, since tendons attach to the fibrous layer of the periosteum and bone only at their distal ends and the tumors under discussion are found, not at this point, but in a position more proximal within the tendon sheaths.

microscopic appearance of these tumors of the patella resembles the giant-cell tumor of the tendon sheaths in regard to the large amount of pink-staining fibroid material. Still more important is the location of these tumors, which resembles the site of origin of similar tumors of the tendon sheath, in that the patella is embedded in a tendon, *being a true sesamoid* bone derived from cartilage.

The immediate inference suggested is

* Smith, D T: Method for making a differential diagnosis between xanthomatous and melanin tumors from frozen sections, Arch. Surg. 8 908, 1924.

Cole, W H.: Primary tumors of the patella, J Bone & Joint Surg. 8 637 1925.

† King, M. J., and Towne, G. S: Primary giant cell tumor of the patella, Arch. Surg 14 892, 1929

that the giant-cell tumors of the tendon sheaths arise in the sesamoid bones. That these bones are derived from cartilage brings this inference into line with the con ception of giant-cell tumor stressed in Chapters 13 and 14, and the occurrence of sesamoid bones more frequently in the ten

logically these bones are cartilaginous bud separating off from the joint side of th future bone just beneath the flexor tendo (Fig. 253) The work of Pfitzner* ha shown that the sesamoid bones are mos frequent on the first, second and fifth digit of the hand and foot at the metacarpopha

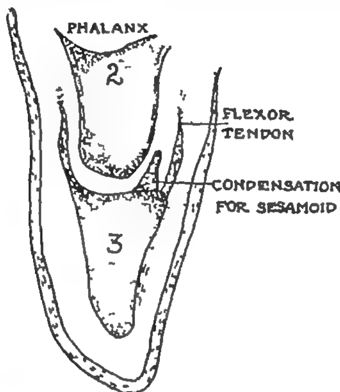


Fig 253 (After Bradley: Anat. Anz. 28: 528.) Sketch showing the development of a sesamoid bone on the flexor side of a digit in a pig embryo 52 mm long of 40 days gestation. The sesamoid bone, preformed in cartilage, is seen budding from the joint side of the distal phalanx.

dons of the fingers coincides with the loca tion of these tumors described clinically

A review of the embryology and anat omy of the sesamoid bones occurring in the human body supports the view that the giant-cell tumor of the tendon sheaths may arise from them. These bones must be re garded, according to Thilenius as integral parts of the skeleton phylogenetically in herited. Bradley† has shown that embryo-

langeal or the metatarsophalangeal join but that they may occur at such sites or t interphalangeal joints in all of the fing and toes. Other but more unusual, sites in the tendons about the elbows, knees ankles and in the tendon of the psoas mus at the pubis or occasionally in the glut maximus near the head of the greater t chapter (Table 42 and Fig. 254)

Thilenius, cited by Bradley O C.: Anat. Anz. 28 528, 1906

† Bradley O C A contribution to the development of the interphalangeal sesamoid bone A Anz. 28 528, 1906.

Pfitzner W Die Sesambeine des Mensch Morphol. Arb.1 517 1892.

In a study of the 27 cases of giant-cell tumors of the tendon sheaths in our own series and in a review of cases reported in the literature, all of those cases having typical giant-cell areas were found to coincide in location with the sites of sesamoid bones. In the cases reported in the literature in which these xanthic tendon sheath tumors do not occupy the site of sesamoid bones, the microscopic reports show that they do not have the typical giant-cell structures and that they belong more properly to the synoviomas, fibromas or ganglia, a point of view confirmed by our studies of more than 300 cases of this variety of tumor in the surgical pathologic laboratory (See Chapter 24.)

The most convincing evidence that the sesamoid bones are the source for these growths, however is indicated by the histology of the tumors themselves, for some vestige of the original structure of the sesamoid bones is usually visible under the microscope.

Special study on this point reveals that the pink-staining network of tissue observed in the sections is the remains of white fibrocartilage, from which tissue the sesamoid bones are derived.

The peculiar yellow color of these tumors that has attracted so much attention differs from the deeper russet color of the giant cell tumor of the long bones because of changes in the blood pigment associated with age. These xanthic tumors have a much longer duration (50 months average duration as compared with 14 months for giant cell tumors of the long bones) Their limited size is due to the small size of the bones affected and the resistance of the fibrous encapsulation, derived from the tendon sheaths. Adjacent bones are eroded on the side opposite the tendon sheaths. This is frequently recorded in the operative notes from many different clinics. In these small bones, compact osseous tissue, which promotes ultimate healing, is wanting, and a slow protracted course is the result.

From the foregoing it is seen that giant cell tumors of the tendon sheaths, which have long been erroneously classed under the heading of xanthomatous lesions, are in reality tumors of the sesamoid bones, rather than of soft parts. These sesamoid bones, which are derived from fibrocartilage, when the seat of giant-cell tumor emphasize again the relation of osteoclastic proliferation in bone newly formed from cartilage to the giant-cell tumor

Treatment The treatment of giant-cell tumors of the tendon sheaths is complete excision rather than enucleation. It must be borne in mind that these lesions are always very cellular and easily confused with

TABLE 42. LOCATION OF SESAMOID BONES IN MAN

In the Upper Extremity	In the Lower Extremity
Flexor surface of the hand	Plantar aspect of the foot
Metacarpophalangeal joint—thumb	Metatarsophalangeal joint—great toe
Metacarpophalangeal joint—index finger	Metatarsophalangeal joint—second toe
Metacarpophalangeal joint—little finger	Metatarsophalangeal joint—little toe
Metacarpophalangeal joint—middle finger	Metatarsophalangeal joint—third toe
Metacarpophalangeal joint—ring finger	Metatarsophalangeal joint—fourth toe
Interphalangeal joint—thumb	Interphalangeal joint—great toe
Interphalangeal joint—index finger	*Interphalangeal joint—rarely second toe*
Other Locations	
Arm Biceps brachii at radial tuberosity	
Leg Patella in quadriceps, peroneus longus at cuboid tibialis anticus at first cuneiform tibialis posticus at talus head of gastrocnemius at lateral condyle of femur psoas at pubis gluteus maximus at greater trochanter ankle tendons at both malleoli	

sarcoma, particularly if infection and recurrence have supervened. It is not unusual to mistake these lesions for malignant pigmented moles, the blood pigment simulating melanin. When recurrence has taken place it is always well to examine the sections from the primary operation to reaffirm the diagnosis of benign giant-cell xanthoma.

Goforth and the other by Stone and Ewing,† with the diagnosis of malignancy in giant-cell tumor No note was made on the presence of the foam cells by these authors, but we observed them in a restudy of the sections.

A review of the nine cases of giant-cell tumor with foam cells brings out nothing of significance other than the perforation

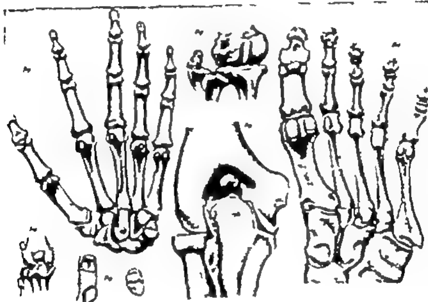


FIG. 254. (After Pfitzner Morphol. Arb 1 517) Anatomic preparations showing sesamoid bones in most of the localities in which they occur on the hand and foot and at the knee and elbow Sesamoid bones occurring about the ankle are not shown in this illustration.

The Xanthomatous Variant of the Giant Cell Tumor of Bone Xanthoma or foam cells appear occasionally in giant-cell tumors of the long bones. In the series of giant-cell tumors (exclusive of those of the tendon sheaths) these characteristic foam cells were found in only nine cases (Fig. 255A) These cells never dominated the picture and were relatively scarce, the tumor in the gross resembling the ordinary giant cell tumor Although a case of xanthosarcoma of bone as described by Ewing has never been observed in our series, we have noted foam cells in two cases of osteogenic sarcoma (Fig. 255B) Both of these cases have been reported in the literature, one by

of the bone shell in these instances. The histology resembles that of the typical giant cell tumor without xanthoma cells. The presence of two recurrent giant-cell tumors and two so-called metastatic giant-cell tumors in this series of xanthoma variants is associated with the perforation of the bony shell by such lesions and not with an increased malignancy The xanthoma cells are formed by the inclusion of lipoids either from organized hemorrhage or from the soft parts about the tendons where the tu

Goforth, J L.: Giant-cell tumor of bone Arch. Surg. 13 846 1926.

† Stone W S., and Ewing, J: An unusual alteration in the natural history of a giant-cell tumor of bone, Arch. Surg. 7 280 1923.

mor is infiltrating, and obviously it is the extent of the destruction of the bony shell and not the chance presence of foam cells that has clinical significance.*

Giant Cell Tumors of the Soft Parts. Because of their relation to the sesamoid bones, a brief note is included on so-called giant-cell tumors of the soft parts. The records of only three such cases are available at this time. Two of these cases are from the surgical pathologic laboratory and one is from the literature. In all of these cases we were able because of the location to relate the tumors to bone.

The condition in the first case was diagnosed clinically as a recurrent mixed tumor of the parotid gland (Fig 256) The patient was a white woman, aged 23 with a tumor near the left ear of three years duration. An incomplete removal of the growth had been performed eighteen months previously and at the second operation a tumor the size of a hen's egg was found wedged in between the mastoid process and the angle of the jaw about the stylomandibular ligament. The pathologic diagnosis at that time was xanthoma of the parotid gland. A restudy of this case four years afterward showed it to be a giant-cell tumor of the styloid process arising from the lower portion of the bone, which has a separate center of cartilaginous ossification, and to which the stylomandibular ligament is attached. Thus the giant-cell tumor tissue was related to cartilaginous bone and the foam cells in the tumor associated with a ligamentous structure.

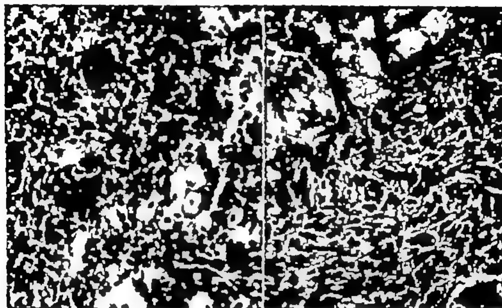


FIG 255 (Nos. 38238 and 40766) Photomicrographs showing (A) xanthoma cells in a typical giant-cell tumor in the lower end of the radius, and (B) xanthoma cells in an osteogenic sarcoma in the upper end of the tibia. The bony shell about the tumor was perforated in both cases.

The other two cases are related by location to sesamoid bones. One of these was described by Mallory * who observed "Foreign body giant cells are sometimes produced in such large numbers in reparative lesions not connected with bone that they may suggest a so-called giant-cell sarcoma. An illustration of such an appearance is given for comparison. The giant cells fol-

* The connection between the foam cells in these tumors and the lipoids derived from the tendons has been confirmed by a study published by Kusnetzowski (Virchows Arch. f. path. Anat. 243: 205, 1927)

* Mallory F B.: Giant cell sarcoma, J M. Research 74: 465, 1911.

lowed some destructive lesion of the fat tissue over the pubes (Plate 28, Fig. 4)" This most extraordinary location coincides with the site of a sesamoid bone in the tendon of the psoas muscle where it glides over the pubic bone doubt that this tumor ever occurs under such conditions.

SUMMARY

Both giant-cell epulides of the alveolar border and some giant-cell tumors of the



FIG. 256. (No. 35631) Photomicrograph of a so-called xanthomatous tumor of the parotid gland. This tumor proved to be a giant cell tumor with foam cells arising from the styloid process of the temporal bone.

tendon sheath are related histogenetically to the resorption of temporary bony structures, and hence despite their extraskeletal location are closely akin to typical giant cell tumors of the bone.

The term epulis is applied to many varieties of lesions upon the gum, but among this miscellaneous collection a clinical entity composed of a giant-cell and fibroid type of epulis may be found. These lesions are common in patients between the ages of 6 and 45 are rare at the site of the molar teeth and generally correspond in location

The last case is similar to Mallory's in that it occurred in the head of the gastrocnemius muscle at the site of a sesamoid bone Under the microscope the remains of the sesamoid bone were clearly visible although the tumor had been diagnosed five years previously as a probable sarcoma of the soft parts.

While we have observed giant cells about bone displacing calcified necrotic tissue in tumors of the soft parts, as in the breast (fat necrosis) we have never found typical giant-cell tumor in such a locality and we

and incidence with the shedding of the deciduous teeth. Pathologically they resemble giant-cell tumor or the giant-cell variants of osteitis fibrosa. They are prone to recur after simple excision unless the excision has been thoroughly done and the region cauterized. The *neighboring teeth* need not be extracted.

Giant-cell tumors of the tendon sheaths are usually related to the development of sesamoid bones rather than to the tendon proper These tumors are usually found in the tendons near the metacarpophalangeal joints but may be found periarticularly in any region where sesamoid bones occur The patients are usually between the ages of 25 and 40 The tumors vary in size from a pea to an egg and the typical yellow color is due to old blood pigment. Microscopically fibrous tissue the remains of white fibrous cartilage giant cells, foam cells and old hemorrhage predominate. Complete excision usually suffices for a cure.

In the long bones the xanthoma variant of giant-cell tumor is relatively rare. These tumors do not differ in their clinical behavior from typical giant-cell tumor but pathologically have a more yellow color and are characterized by the presence of foam cells and other evidences of lipoid degeneration.

Most of the so-called giant-cell tumors of the soft parts may be related to aberrant sesamoid bones or to heterologous centers of ossification involving precartilaginous tissue.

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16

Variants of Neoplastic Ossification

OSTEOID OSTEOMA

In 1935 Jaffe called attention to a small rarefying lesion in the enchondral bones composed of vascular fibrous tissue and proliferating osteoblasts, in which were embedded minute spicules of newly formed osteoid spicules. This lesion usually occurred in young adults with localized pain and swelling of the bone simulating a Brodie's abscess. He gave it the name of osteoid osteoma. Examples of osteoid osteoma were classified in an earlier edition of this book as atypical giant-cell tumor.

In 1940 Jaffe was able to collect 33 cases. The peak of age incidence was between 11 and 24 years. Twenty cases occurred in the long bones of the extremities, nine in the small bones of the hands and feet, one in the patella, and three in the vertebrae. The duration of symptoms averaged over a year and varied from 7 to 24 months. The clinical symptoms of localized pain and swelling and the roentgenologic features of a small rarefied lesion overlaid by sclerotic bone led to a clinical diagnosis of inflammation in almost every case. The most frequent diagnoses prior to operation were (1) nonsuppurative osteomyelitis, (2) syphilitic ossifying periostitis, (3) Brodie's abscess, (4) subacute osteomyelitis with annular sequestrum.

Under the microscope, spicules of calcified osteoid tissue appear in a vascular connective-tissue stroma. The process can occur either intracortically or in the spongiosa. When located within the cortex, the overlying bone is thickened and eburnated through the reaction of periosteal and endosteal new bone. The perifocal reaction is not marked when the lesion is in cancellous bone.

The cases studied by Jaffe and Lichtenstein were cured by simple excision and recurrence has not been recorded.

Following Jaffe's description of osteoid osteoma, the authors were able to segregate from their files ten cases of osteoid osteoma. The majority of these had been previously diagnosed as healing intracortical abscess, and had occurred in the shaft of the tibia or femur (Fig. 257.) The small rarefied lesions were surrounded by an extensive sclerosing reaction in the cortex. In one case followed on the wards for over a month, the cortical reaction only was visible at first and only after a matter of three weeks was the small circular translucent area depicted in the roentgenogram (Fig. 258). Two cases occurring in the os calcis and one in the phalanx of the hand had been diagnosed as atypical giant-cell tumors with a marked healing reaction. (Fig. 259.) Two other cases occurring in the bones of the jaw had been classified as ossifying fibromas (Nos. 46392 and 39620). These were in the mandible and zygoma, beneath a thin shell of cortical bone.

In the cases we have studied, the clinical

features agree with those emphasized by Jaffe and Lichtenstein The patients are young adults or adolescents. There is localized pain and tenderness without fever or leukocytosis. The lesion is chronic and of several or more months duration.

Sherman has reported two cases of osteoid osteoma associated with arthritic symptoms in the neighboring joints. In one patient, the lesion was in the neck of the femur and the hip joint was painful. In the other the lesion was in the humerus in the olecranon fossa, and the elbow joint was painful. There was no systemic reaction. There was increased joint fluid. The synovial membrane of the hip joint showed thickening and proliferation. In both cases, culture and guinea pig inoculation of the fluid were negative. The joint symptoms subsided following removal of the tumor by curettage.

Voshell and Appleby reported a case of osteoid osteoma of the proximal portion of the femur in which there was an associated myositis ossificans in the adjacent psoas muscle. In one of our cases (Fig. 260) there were cartilaginous rests in the metatarsal bone associated with an osteoid osteoma of the os calcis.

In the roentgenogram the lesion is either in the cancellous portions of one of the small bones, such as those of the hand, foot or vertebra, or has an intracortical location in the shaft of a long bone, such as the tibia or femur When occurring in spongy bone, a perifocal condensation of new bone is usually not stimulated, but when occurring within the cortex of a long bone there is a zone about the lesion of compact newly formed cortical bone. The lesion itself is radiolucent and is always of small size (less than 2 cm. in diameter) It can be diagnosed when occurring in cancellous bone by these features of radiolucency and limited



Fig. 257 Osteoid osteoma occurring intracortically in the shaft of the tibia. Both the roentgenogram and the photomicrograph show characteristic features. The roentgenogram shows an intracortical area of rarefaction, with perifocal sclerosis. The reactive sclerotic area far exceeds the radiolucent lesion, which represents the osteoid osteoma. The photomicrograph shows the osteoid spicules being laid down by proliferating endosteal tissue which is composed of fibroblasts, osteoblasts and numerous thin-walled blood vessels.

circular size. When occurring in the long bones, it occupies the cortex and presents the same minute rarefied, circular lesion, but about it there is a marked reaction of dense new bone which extends for one-third to one-half the length of the shaft.

In the early and active phases of osteoid osteoma, there is a proliferation of vascular skeletal mesenchyme with a profusion of osteoclasts and osteoblasts. In this phase the preformed cancellous or cortical bone undergoes resorption by the growth of pathologic tissue. As the lesion develops, osteoid spicules surrounded by numerous osteoblasts and fibroblasts are formed in a closely knit pattern, with persistence of the vascular mesenchyme. The osteoid spicules calcify and may become laminated. They do not, however, grow to large size and do not form the open trabecular network of normal cancellous bone nor do they solidify into the broad bands of solid bone typical of the normal cortex. The outstanding features of the pathologic process are the absence of cartilage formation (in most cases) the failure of the osteogenic process to form mature osseous structures, and the limited size of the lesion.



Fig. 258. Roentgenogram showing a typical case of osteoid osteoma of the tibia.





Fig. 259 (*Left*) Roentgenogram of osteoma occurring in the proximal phalanx of the fourth finger. (*Right*) Photomicrography of a giant-cell tumor in the phalanx of a toe. Portions of trabeculae of cancellous bone are undergoing absorption, while the proliferation of fibroblasts in other areas shows a healing reaction.

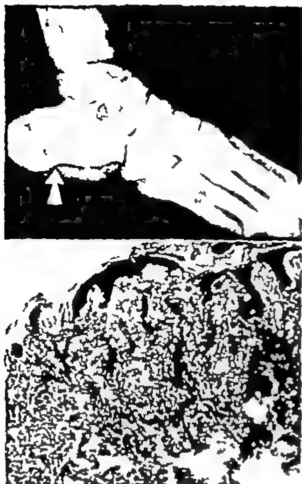


FIG. 260 Osteoid osteoma. (A) Roentgenogram shows a radiolucent lesion in the os calcis, surrounded by the characteristic zone of sclerosis. The patient complained of pain in his heel of three months duration. Note the cartilaginous rests in the metatarsal bone. (B) Photomicrograph shows vascular osteoid osteomatous tissue surrounded by trabeculae of newly formed bone

Treatment Excision suffices to cure these small benign lesions. The surrounding eburnated reactive bone often chisels with difficulty and unless successive chips are examined, the lesion may be overlooked. It is usually a small spongy zone located in a portion of the excised sclerotic bone.

PATHOGENESIS OF OSTEOID OSTEOMA

The type of ossifying connective tissue found in osteoid osteomas is not peculiar to these lesions. A phase of reossification following the resorption of calcified cartilage is found on the metaphyseal side of the epiphyseal plate in all of the growing long bones from fetal life through adolescence. Similar histologic pictures are found at times in Paget s osteitis deformans, in a phase of growth of osteomas of the skull and jaws and more rarely in cases of myositis ossificans.

Yet in osteoid osteomas there are several distinctive features of the ossifying process: (1) A cartilaginous phase usually is not observed although the lesion occurs most frequently in the enchondral bones. (2) Mature spicule formation has not been reported in spite of the chronic nature of the process which extends over a period of six months to two years in many cases. (3) The lesion is practically always solitary and of minute size, the average case being under 1 cm. in diameter. (4) Although the intracortical osteoid osteomas stimulate a marked perifocal ossification of dense cortical bone this cortical bone never invades or obliterates the initial lesion (as far as can be determined to date) and the two types of ossification remain sharply delimited one from the other

On the basis of morphology alone it would appear that one of two things would have to happen in the typical osteoid osteoma located within the cortex of the shaft of the long bone Either the marked periosteal new bone should overwhelm and obliterate the minute rarefied lesion, or the active vascular osteoid osteoma should invade the eburnated cortex and produce a progressively larger area of destruction of normal bone. Neither has yet been observed. As a matter of fact, some authors think that both occur and that the osteoid osteoma is a phase of focal, low-grade inflammation in bone. If left alone, the regressing osteoid osteoma should pass into a sclerosing osteitis or ossifying periosteitis. On the other hand, if the lesion progresses, it should develop into a Brodie s abscess This was essentially the opinion of Phemister but he could not verify this by bacteriologic cul

tures nor could Jaffe and Lichtenstein prove an inflammatory origin.

Another unverified interpretation holds that the osteoid osteoma represents a healing area of bone infarction of minute size. The embolic occlusion of a small vessel should be demonstrable in early cases and it should be possible to produce these lesions experimentally by injecting particulate matter into the nutrient vessel of a long bone in animals.

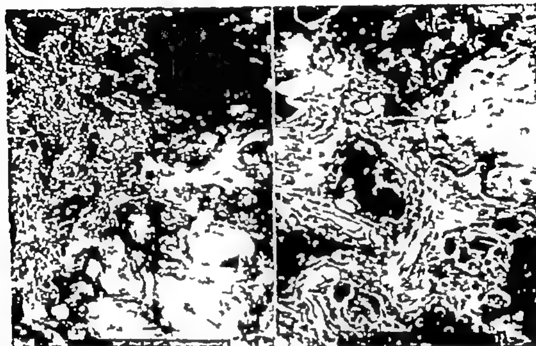


Fig. 261 (No 42199) Low and high-power photomicrographs of osteoid osteoma. Sections show an area of cartilage which is being converted into bone by creeping substitution. Cartilage in osteoid osteomas is exceedingly rare

PROGRESSIVE AND TRAUMATIC MYOSITIS OSSIFICANS

Various forms of myositis ossificans have been described. The progressive diffuse form, which begins in children with other congenital defects, such as microdactylism, and involves successive muscles beginning usually in the trapezius or latissimus dorsi, is shown in Figure 283. Unlike traumatic myositis, the disease is as common in females as males. It was first described by Guy Patin in 1692. Rosenstirn was able to collect 119 cases of progressive myositis ossificans in 1918. Trauma may be the initiating factor in starting the long sequence of debilitating events. In our two cases the onset of the disease was in the sixth and tenth years and both were females. The lesions began in the thoracic portion of the

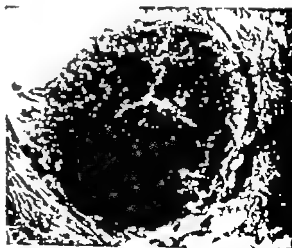


Fig. 262. Low power photomicrograph of an osteoid osteoma occurring in a phalanx of the toe



Fig. 263 (No 56333) Roentgenogram of a case of myositis ossificans, progressive type, showing ossification in the tendons at the lower end of the scapula and at the origin of the serratus muscle.

spine and rapidly became multiple. It is a rare disease, running a slow but progressive course. Motion at the joints is restricted by the osseous deposits which gradually



FIG. 264. A case of myositis ossificans secondary to operative removal of an exostosis, in which muscle ossification simulated the cartilaginous cap ordinarily found surmounting the spicule.

infiltrate all of the soft tissues in the vicinity of bone. The patients ultimately are bed ridden and succumb to intercurrent infection.

A decalcifying diet (elimination of milk, cheese and eggs) and the administration of magnesium carbonate by mouth (a tablespoonful three times a day after meals) may result in improvement, but there is no specific form of therapy

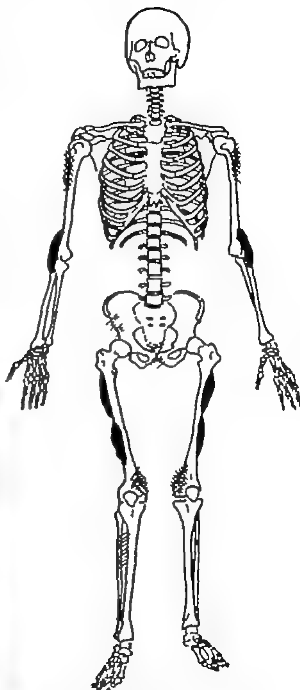


FIG. 265 Chart showing the incidence of myositis ossificans according to skeletal location. The solid black areas indicate the most frequent sites the checked areas, the common sites, the diagonal line areas, the occasional sites.



Fig 268. A gross specimen of myositis ossificans, presenting cystic changes.

CIRCUMSCRIBED TRAUMATIC MYOSITIS OSSIFICANS

Varieties of the circumscribed type of myositis ossificans are generally classified under the traumatic and nontraumatic forms, of which the traumatic type is by far the more frequent. The trauma may be single or repeated, due to some occupational habit. The occupational form was the first described (Billroth 1855) under the term "rider's bone," and later under the term "drill bone," both of which are common among enlisted men in the cavalry and infantry respectively. The ossification of the deltoid muscle, due to the rifle, and of the adductors in the thigh, due to the pressure of the saddle, has been termed the "Prussian disease," since so many of the reports have come from that country (Küttner)*

In this country traumatic myositis ossificans of the circumscribed type is most frequent following a single injury and is seen following posterior dislocation of the elbow producing ossification in the brachialis anticus, and injuries of the quadriceps femoris in football players. Among the 30 cases of this form of circumscribed myositis ossificans recorded in our series, involvements of these two muscles predominate (Fig. 265) Patients between the ages of 20 and 40 are in the majority the maximum age in this series being 43. Cases occurring under 20 are not rare, but in more elderly patients are unusual. Females are very rarely affected—only once in our series. The

* Küttner Hermann: Die Myositis ossificans circumscripta, Ergebn. d. Chir u. Orthopadie 1: 49, 1910.

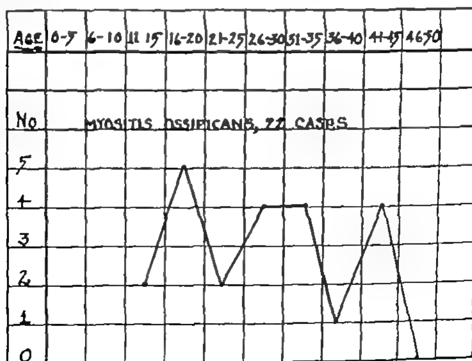


Chart 9 Showing the age incidence of myositis ossificans.

history is characteristic. Following a severe injury there is hemorrhage into the muscle, with the formation of a hard tumor with ossification within a period of from three to six weeks. The injury is commonly received either in football or accidentally in some occupation, such as mining mill-working, etc.

In the roentgenogram there is a single lesion showing a more or less wedge-shaped area of laminated bone, separated from the normal bone by a definite interval of soft parts throughout most of its length. The edges are usually smooth and well outlined and the location is commonly near the elbow or in the thigh. Dean Lewis emphasizes a tendency for the area of ossification to attain its maximum rapidly and then to remain stationary or decrease. The diagnosis of such a lesion roentgenographically when there is a definite history of trauma, is not difficult. However variations of this picture occur in which the wedge of new bone may adjoin the shaft of the normal bone beneath, and one free edge may be extremely irregular. The irregular edge, infiltrating the muscles, may assume the characteristic of the so-called dotted veil, while the fact that new bone occurs only at one side of the normal bone, and does not surround it, is helpful in diagnosis (Fig. 287). Rarely the ossification may be extensive and simulate osteogenic sarcoma, as in the cases of Chambers, Paul,* and one of Coley's.† The resemblance of such a form of myositis ossificans to sarcoma is not only apparent but real, since a small percentage of these cases with extensive irregular ossification become malignant after an interval of years, recurring in spite of excision, to produce ultimate metastases and death. Pack and Braund reported two cases of traumatic myositis ossificans which underwent sarcomatous change. One of these was in a man of 36 years who had had the ossifying mass for 15 years. The malignant growth was cystic and hemorrhagic on removal. The recurrence was diagnosed as osteogenic sarcoma. The patient died with metastasis 13 months later. The second was a man age 27 in which a tumor mass 2 cm. in diameter was removed from the right thigh in 1934. This recurred within 7 months and again 18 months after the first operation. Pulmonary metastasis and cerebral metastasis occurred and the patient died approximately 3 years after the first operation. In a third case sarcoma developed in progressive myositis in a boy of 7



FIG. 287. Roentgenogram of a case of myositis ossificans showing the typical laminated structure of the bone deposits and the so-called "dotted-veil" appearance.

* Paul, John R. Case of periosteal fibroma followed by progressive myositis ossificans, Proc. Path. Soc. Phila. 24: 89. 1923–1924.

† Coley, William B. Myositis ossificans traumatica: a report of three cases illustrating the difficulties of diagnosis from sarcoma, Ann. Surg. 57: 305, 1913.



FIG. 268. (No 43036) Photomicrograph of new bone formation proceeding from fibrous tissue without the presence of cartilage, typical of the majority of cases of myositis ossificans.



FIG. 269 Roentgenogram of a typical myositis ossificans. This lesion occurred six weeks after an injury The osseous mass is parallel to the shaft of the femur It is contiguous to it but does not overlap it.

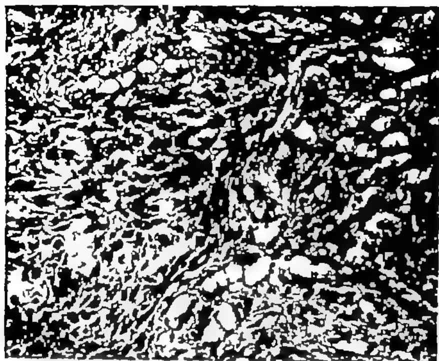


FIG. 270 Photomicrograph (medium magnification) of pseudomalignant tissue in myositis ossificans.



FIG. 271 Photomicrograph showing confluent areas of osteoid trabeculae and cartilage in myositis ossificans.

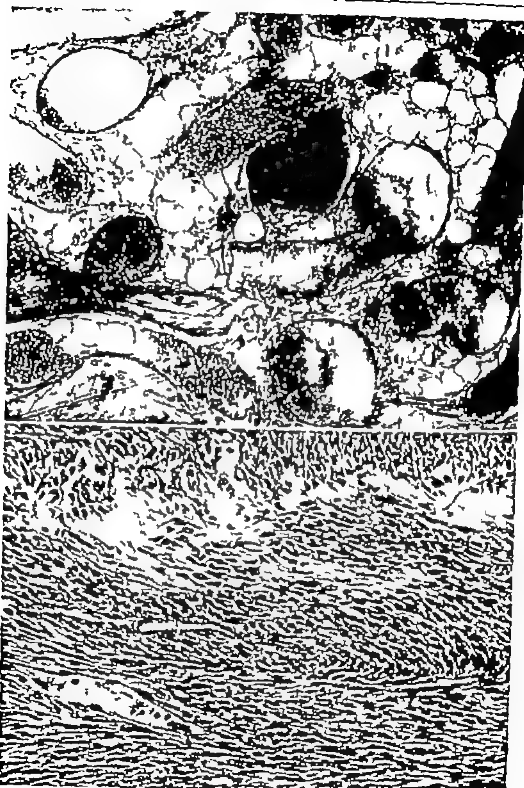


FIG. 272. (*Top*) Photomicrograph (medium magnification) of bone formation about capillary walls. (*Bottom*) Photomicrograph of myositis ossificans which metastasized to the lungs and terminated fatally



Fig. 273 Roentgenogram and gross specimen of a benign osteoma occurring in the subpatellar bursa. The patient was a man aged 59 who attributed the tumor to a dislocated knee 10 years previously. There had been pain and limp for 2 years.

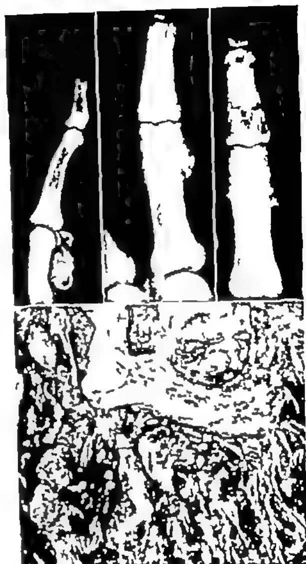


Fig. 274 Roentgenogram and photomicrograph of an osteochondroma occurring in the tendon sheath on the flexor surface of the proximal phalanx. The lesion is separate from bone.

Shipley found four cases recorded in the literature in which osteogenic sarcoma complicated myositis ossificans. There are two cases in our series, one in the deltoid and one in the gastrocnemius.

Histologenetically the source of the new bone is fibrous strands in the muscle, or tags of precartilaginous embryonic connective tissue (blastema) displaced from the primitive periosteum however the reason for the heterologous ossification at these sites in the muscle is obscure. A hematoma seems to be an important antecedent to the ossification. Dean Lewis emphasizes periosteal stripping by injury as a source of the new bone. This would account for some types which show direct ossification of the membranous type, but would not account for the myositis ossificans derived from cartilage, which must involve strands of blastemal tissue. The dotted veil appearance in

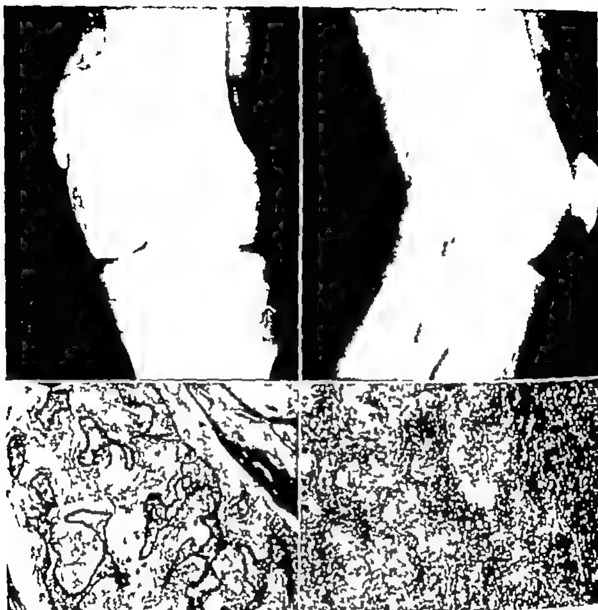


FIG. 275 Roentgenograms and gross specimens of a cellular parosteal osteoma occurring near the medial condyle of the femur The tumor occurred in a boy of 19 years. The parosteal growth was excised, but the tumor recurred in the underlying periosteum and invaded the femur An amputation was performed for the recurrence.

the roentgenogram, extending out into the muscle, is against the assumption that periosteum of any extent has been displaced, since, *as a limiting* membrane of ossification, it tends to produce more circumscribed bone formation More recent experiments seems to indicate that the stimulation to ossification is chemical, in the form of increased calcium deposition at the local site, in the presence of an injured vascular supply

The microscopic pictures which myositis ossificans may present are important because of the tendency to confuse the lesion (following exploration) with sarcoma. The roentgenographic picture is usually diagnostic, but atypical cases are frequently explored and the pathologic report requested from the laboratory without affording the pathologist the opportunity of correlating the histologic picture with the clinical findings. If the bony trabeculae



FIG. 276 Roentgenograms of parosteal osteoma. Note that the lesion appears discrete and separated from the femur in the lateral view but in the anterio-posterior view it involves the adjacent femur



FIG. 277 Roentgenograms of parosteal osteoma undergoing malignant change. Symptoms of the growth had been present for 10 years before the lesion was discovered by roentgen examination. At this stage the tumor has the appearance of an ordinary osteogenic sarcoma. Under the microscope however it was seen to be composed of cellular connective with minimal amounts of osteoid substance. An amputation was performed.



FIG. 278. Roentgenograms of a par osteal osteoma occurring in a girl of 25 Pain and limp were present for two months (*Left*) Lesion before operation in March, 1945 (*Right*) Lesion in January 1948. The growth has remained stationary (Jan 1949) following exci sion of the extra-osseous mass and post operative irradiation

are well separated from each other and embedded in adult or edematous fibrous tissue with a solitary intervening row of osteoblasts, the diagnosis is easy Lami nated bony spicules embedded in angioma tous tissue is likewise difficult to confuse with sarcoma. But cellular connective tis sue, with imperfect osteoid trabeculae which contain persisting osteoblasts rather than osteocytes, is easily confused with osteogenic sarcoma. (Fig 270) Cartilage overlaid by calcified areas adjoining oste oid spicules is also found, and the cartilage may simulate that seen in chondrosarcoma. As pointed out above, malignant change may rarely occur and the differential diag nosis under the microscope may tax the judgment of the most experienced pa thologist.

The prognosis in these cases is usually favorable. The symptoms attending the os sification may subside spontaneously or if persistent, will usually disappear after the bone formation has become stationary

Treatment The best treatment is watch ful waiting

It is a mistake to intervene surgically in the early stages of this condition while os sification is still in progress, since the growth may be stimulated and recurrence may result. A more conservative and ex pectant attitude is to be recommended in view of the unhappy surgical results occa sionally recorded.

PAROSTEAL OSTEOMA OR MYO-OSSEOUS OSTEOMA

One of the authors (C. F G) has ob served 10 cases of ossifying fibrous tissue which extends into the soft parts, beside the bone, suggesting a circumscribed myositis ossificans but involving the neighboring bone as well (Fig 275) or is confined en tirely to the soft parts. In the roentgeno gram, there is an ossifying mass, usually the size of a fist. The region of the lower femur is a frequent site. The tumor ex tends either laterally or into the popliteal space and is for the most part separated from the bone, like myositis ossificans. The adjacent bone, however in the progres sively growing types, forms a platform with an irregular border and in some of the views the mass appears continuous with the bone. Microscopically the lesion suggests a cellular myositis ossificans. There are bony trabeculae embedded in fibrous tissue, with nests of giant cells. Elsewhere, the fibro blasts, osteoblasts and giant cells are in termingled, suggesting osteolytic sarcoma, but the nuclear detail is that of a benign lesion Some of the growths contain small amounts of cartilage.

The lesions progress slowly with the symptoms of tumor tenderness, pain and dysfunction. When the growth is embedded entirely in a tendon, a stationary stage is reached and the symptoms may subside. (Fig 274.) In the larger and more progres sive growths, after a period of years, the roentgenogram suggests a sclerosing osteo genic sarcoma (Figs. 275, 277) When the lesion is explored, however it is difficult to



FIG. 279 Photomicrographs of the tumor shown in Figure 278. The tissue has the appearance of myositis ossificans but it involves underlying bone.

find anything but cellular ossifying fibrous tissue. In one case the popliteal mass was present eleven years. At the end of this time roentgenograms suggested osteogenic sarcoma and amputation was performed. However repeated sections of the specimen demonstrated only cellular fibroblastic proliferation with osteoid substance. In a re-

It is difficult to distinguish these ca from rare forms of myositis ossificans und going malignant change.

Treatment If the underlying bone is extensively invaded, excision is perform When the benign character of the tissu confirmed by microscopic examination single course of postoperative irradiat



Fig. 280 Photomicrographs of osteogenic sarcomas of extraskeletal origin. (*Left*) Thyroid. (*Right*) Breast.

cent case of a girl of 25 the mass next to the bone was excised, leaving a roughened, indurated periosteum and an eroded cortex. Malignancy could not be demonstrated microscopically In the gross, the tissue suggested myositis ossificans. However the lesion in the underlying bone continued to progress, with expansion of a thin shell of cortical bone The lower femur which was the site of the lesion, received two courses of irradiation, each about 3 000 r There has been no change roentgenographically in the past three years and the patient has full use of the limb without pain or tenderness. The ultimate prognosis, however is grave, since renewed growth has ultimately occurred in our cases.

is given. The lesion is then followed repeated roentgen examination at inter of six months. If renewed growth is amputation is performed.

EXTRASKELETAL OSTEOGENIC SARCOMA

Heterologous or so-called metaplastic ssification has been described in practic all organs of the body where connec tissue is found. It occurs in the wall blood vessels, heart, in the bladder kidr breast, uterus and in the soft parts ge ally This type of heterologous ossifica is often looked upon as a reparative p ess in an area of tissue necrosis w calcium has been deposited. In such

TABLE 43

Author	Patient and Complaint	Essential Characteristics of Lesion
Arnold	Woman age 67 Goose-egg size tumor of nipple for [illegible] months.	Spindle and giant cells. Islands of cartilage and of osteoid tissue No mention of metastases No follow-up after operation. DIAGNOSIS Osteochondrosarcoma of breast
Bianchi	Woman, age 60 Tumor in right quadrant of abdomen. No jaundice.	At operation a malignant tumor of gallbladder was removed Gallbladder contained stones Tumor arising from fundus showed spindle cells and osteoid tissue and calcification. Numerous mitotic figures. DIAGNOSIS Osteogenic sarcoma of gallbladder
Broders and Pemberton	Woman, age 71 Growth in right side of neck for 4 months.	Biopsy Pleomorphic and spindle cells. Areas of osteoid and tumor bone present. Radium needles inserted. Patient eventually died of sarcoma. DIAGNOSIS Osteogenic sarcoma of the thyroid
Budd and Breslin	Woman, age 59 Lump in chest wall above breast for 28 years. Rapid growth for past year	No roentgen examination. Hard tumor calcified in some areas Microscopic Some areas showed carcinoma cells with alveolar structure. Other areas contained spindle cells, osteoid tissue and bone. One type of tissue merged with the other Numerous mitotic figures. DIAGNOSIS Carcino-osteogenic sarcoma of chest wall.
Busser	Woman, age 60 Radical mastectomy Recurrence 2 years later	Microscopic at first operation showed adenofibroma with some osteoblasts and chondroblasts at the periphery Recurrence of nodule in scar 2 years later Immature cells rapidly growing. Chondroblasts and osteoblasts. Osteoid tissue. Definitely malignant. DIAGNOSIS Osteochondrosarcoma of breast.
Butler and Woolley	Woman, age 68. Tumor left thigh 11 years. Before bruised leg at this site and some swelling, had persisted	Roentgen findings Soft-tissue mass 9 × 5 cm Periphery of mass showed areas of irregular calcification suggestive of an "old calcified hematoma." Tumor excised 20 × 12 × 10 cm Microscopic Round and spindle cells mitotic figures, some calcium and some true bone Chest metastases present upon roentgen examination. Died 2 years after onset. No autopsy DIAGNOSIS Osteogenic sarcoma arising from calcified hematoma.
Caen	Woman age 59 Tumor of breast, size of child's head."	Hyalin cartilage and bone present. DIAGNOSIS Osteochondrosarcoma.
Chavannaz and Pierre-Nadal	Woman, age 74 Tumor of thyroid present several years rapid growth for 2 months.	Tumor composed of spindle cells cartilage and bone. DIAGNOSIS Osteogenic sarcoma of the thyroid.
Ferrero	Woman, age 29 Tumor of abdominal wall 2 months	Tumor size of "hen's egg," excised from lower abdominal wall. Recurred and radical excision performed. Microscopic Very cellular—round, oval, and spindle cells Interlacing trabeculae of bone and osteoid tissue. DIAGNOSIS Sarcoma.

Harwell Wilson, Extraskeletal ossifying tumors, Ann. Surg 113 97-98, 1941

find anything but cellular ossifying fibrous tissue. In one case, the popliteal mass was present eleven years. At the end of this time roentgenograms suggested osteogenic sarcoma and amputation was performed. However repeated sections of the specimen demonstrated only cellular fibroblastic proliferation with osteoid substance. In a re-

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Fig 280 Photomicrographs of osteogenic sarcomas of extraskeletal origin. (*Left* Thyroid. (*Right*) Breast.

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Budd and Breslin	Woman, age 59 Lump in chest wall above breast for 28 years. Rapid growth for past year	No roentgen examination. Hard tumor calcified in some areas. Microscopic Some areas showed carcinoma cells with alveolar structure. Other areas contained spindle cells, osteoid tissue and bone. One type of tissue merged with the other Numerous mitotic figures DIAGNOSIS Carcino-osteogenic sarcoma of chest wall.
Bumer	Woman, age 50. Radical mastectomy Recurrence 2 years later	Microscopic at first operation showed adenofibroma with some osteoblasts and chondroblasts at the periphery Recurrence of nodule in scar 2 years later Immature cells rapidly growing Chondroblasts and osteoblasts. Osteoid tissue. Definitely malignant. DIAGNOSIS Osteochondrosarcoma of breast
Butler and Woolley	Woman, age 65. Tumor left thigh 11 years. Before bruised leg at this site and some swelling, had persisted.	Roentgen findings Soft-tissue mass 9 × 5 cm. Periphery of mass showed areas of irregular calcification suggestive of an old calcified hematoma." Tumor excised 20 × 12 × 10 cm Microscopic Round and spindle cells mitotic figures, some calcium and some true bone Chest metastases present upon roentgen examination. Died 2 years after onset, No autopsy DIAGNOSIS Osteogenic sarcoma arising from calcified hematoma.
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Harwell Wilson, Extraskeletal ossifying tumors. Ann. Surg. 113 97–98, 1941

TABLE 43 (*Continued*)

Author	Patient and Complaint	Essential Characteristics of Lesion
Foerster	Woman, age 60. Tumor of thyroid. Duration not given.	Spindle cell bone present in tumor. No metastases. DIAGNOSIS Osteogenic sarcoma of thyroid.
Funkenstein	Tumor of thyroid	Spindle cells. Bone present. No metastases. DIAGNOSIS Osteogenic sarcoma.
Funkenstein		Similar to above case
Gomori	Woman, age 64. Painless lump in right breast for 6 months. Size of baby's head", ulceration.	Simple mastectomy and resection of axillary nodes. Spindle cells, giant cells, mitotic figures, boney trabeculae present. DIAGNOSIS Osteochondrosarcoma of breast.
Haining and Poole	Man, age 76. Hematuria, mass in left kidney region.	AUTOPSY Tumor of left kidney which, histologically was said to be identical with osteogenic sarcoma. Spindle, round and giant cells present. Osteogenic tissue and bone. Widespread metastases. Some metastases contain bone
Jaidka	Boy, age 14. Pain and stiffness, in right thigh for 6 weeks. Tumor in vastus externus.	Hip joint disarticulation. Malignant tumor of fibrous tissue origin present producing bone. DIAGNOSIS Ossifying sarcoma of vastus externus muscle.
Kreibig	Woman, age 50. Walnut-size tumor of breast.	Giant cells, cartilage, osteoid tissue and bone. DIAGNOSIS Osteosarcocarcinoma of breast.
Kubo	Man, age 39. Tumor right side of abdomen.	GI roentgenogram only. Explored tumor "size of head" adhered to bowel and peritoneum. Lymph node biopsy showed fibrosarcoma. Autopsy 55 days later: osteofibrosarcoma of mesentery. Large areas of bone. Some myxomatous tissue
Kurosu	Woman, age 60. "Head-size tumor" of breast, duration not given.	Died soon after excision. DIAGNOSIS Osteochondro-angiosarcoma. No autopsy
Mallory	Woman, age 55. Breast tumor for 3 months.	Tumor excised. Recurred. Microscopic: composed of spindle cells. Tumor giant cells present. Bone trabeculae. Frankly neoplastic process. Bone probably heterotopic, possibly neoplastic. DIAGNOSIS Sarcoma of thigh containing bone
Pick	Woman, age 51. Tumor present in neck for several years. Developed tumor of palate and died soon afterwards.	Tumor of neck was sarcoma in thyroid. Mass made up of spindle cells. Bone present in many areas. Widespread metastases. Lung metastases contained bone. No autopsy
Rhoades and Blumgart	Woman, age 21. Lump in right thigh for 5 weeks.	Encapsulated tumor not connected with thigh. Microscopic: spindle cells, mitoses, osteoid changes into bone. Well 10 years later. DIAGNOSIS Osteoblastoma.
Rhoades and Blumgart	Male, age 37. Swelling in left groin for 15 months.	Left inner thigh firm, rounded mass 2 × 6 cm. X-ray: Calcium density in region of tumor. Microscopic: immature fibroblasts, many mitoses, new bone, osteoid tissue and cartilage. Well 7 years after excision. DIAGNOSIS Osteoblastoma.

TABLE 43 (Continued)

Author	Patient and Complaint	Essential Characteristics of Lesion
Sailler	Woman, age 50 Lump in right breast for six week	Tumor present 4 × 3 cm Microscopic spindle round cells. Many mitoses. Spicules of bone surrounded by osteoblasts. Osteoid and cartilage present. Well 2 years later DIAGNOSIS Sarcoma of breast. (Osteogenic)
Sehrt	Woman age 44 Fist-sized" tumor of breast for six months.	Excised. Microscopic giant cells, cartilage osteoid and bone present Appearance of bone varied considerably in various areas of the tumor No mention of metastases. No follow-up DIAGNOSIS Osteosarcoma of breast
Stilling	Woman age 53. Large breast tumor Duration not given	Osteoid tissue cartilage and bone in tumor Metastases to lungs. DIAGNOSIS Osteosarcoma of breast
Stilling	Woman, age 50 Tumor of breast	Osteoid tissue and cartilage spindle and giant cells Local recurrence 5 weeks after excision Metastases to distant foci. DIAGNOSIS Osteosarcoma of breast
Solaro	Male age 46 Tumor of thyroid region for 8 months.	Spindle cell sarcoma of thyroid contain much bone and cartilage Boney tissue appeared to be rather normally formed. Recurred 2 months after operation DIAGNOSIS Sarcoma of thyroid, osteogenic."
von Hacker	Woman, age 80. Small tumor of left breast for 20 yrs. Rapid growth for 1 month.	Cartilage bone fibrous tissue and osteoid tissue Believed to be carcinoma containing bone
William	Woman, age 53 Tumor in calf muscles for 10 months.	Hard tumor in gastrocnemius ROENTGEN FINDINGS Irregular shadow of calcium density Partially encapsulated at operation Arose from fascial plane between gastrocnemius and soleus. DIAGNOSIS Round cell sarcoma forming new bone

tions it does not have the growth tendencies of a neoplasm. The ossification proceeds directly from fibrous tissue. When adult bone is formed, the cancellous spaces contain bone marrow Cartilage is absent, as a rule.

There are, however examples of extraskeletal ossification which must be looked upon as truly neoplastic and in which malignant change usually supervenes. These lesions have the histologic aspect of osteogenic sarcoma and frequently contain cartilage.

Extraskeletal malignant ossifying tumors are extremely rare but among the recorded cases the predominant locations are breast, thyroid, kidney and soft parts. The authors have previously reported three cases of osteogenic sarcoma occurring in the mammary gland. These were in elderly patients between the ages of 65 and 70 years. Wilson has tabulated a series of 29 cases of extraskeletal ossifying tumors, of which 12 were located in the mammary gland. The thyroid is probably second to the breast as a site for malignant heterologous ossification. We have the records of two such cases and Wilson has tabulated six others. The additional sites for aberrant osteogenic sarcomas are the uterus (three times in our cases) the kidney the abdominal wall, chest wall thigh, neck, groin and calf muscle and the gall bladder

The tabulation of the cases compiled by Wilson is given here through his kind permission.

These cases of aberrant osteogenic sar

coma are progressively growing and infiltrating malignant growths which terminate fatally as a rule in spite of radical excision. They are radio-resistant and have about the same growth potentiality as fibrosarcoma arising in the stroma of the organ affected. The treatment of choice in these cases is radical removal of the organ affected.

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PART THREE

Tumors of Nonosseous Origin

ORIENTATION

While most of the neoplasms of bone can be readily associated with phases of devel opment there is another group of tumors not arising in osteogenesis which involve marrow vessels, or overlying fibrous tissues or secondarily invade the bone from other organs.

These growths of nonosseous origin in clude Ewing's endothelial myeloma, which arises possibly from the lymphatics of bone multiple myeloma, a neoplasm derived from the marrow tissue, metastatic carcinoma arising elsewhere in the body and finding its way to bone via the blood stream or lymphatics, and the so-called periosteal fibrosarcoma arising in the neighboring fascia, the nerves or the outer layer of the periosteum.

Only two of these, Ewing's tumor and multiple myeloma, can be regarded as true entities, the former having been separated by Ewing in 1924, the latter by Rustizky Kahler and Bozzolo between 1873 and 1887 The other two comprise either types of carcinomas of the viscera and other organs metastasizing to bone, or sarcoma of the neighboring soft parts invading bone by direct extension

17

Ewing's Sarcoma

HISTORICAL BACKGROUND

In the original descriptions of Ewing's sarcoma this neoplasm was placed among the endotheliomas. This term, which was introduced by Golgi in 1869 met with unusual favor as a convenient pigeonhole for many odd and unusual tumors, the origin of which is not clearly understood. Billroth in 1856 Waldeyer† and Kolaczek‡ in 1878, and 1880, gave a comprehensive description of such tumors placing cylindromas and angiosarcomas in this group The term perithelioma has also been used for many malignant tumors, such as certain types of angiosarcoma, the term being given special prominence by Hildebrand§ in regard to certain tumors of bone

In regard to such classifications, Ribbert‖ expressed the view that the endothelial origin of tumors of the bone has yet to be proved, and further that the mere continuity of the tumor cells with endothelial structures at the margin is no proof of their identity In recent years, Ewing adopted the conception of Borst that the scope of endothelioma is probably wide and he selected a nonosteogenic tumor of bone with many clearcut clinical features, classifying it as endothelial myeloma† or diffuse endothelioma‡ of bone Conner,§ in a study of the material with the Bone Registry of the American College of Surgeons, supported Ewing. Kolodny ‖ in a similar treatise, agreed that the tumor presents a clearcut entity but did not feel that the contention that it arises from perivascular endothelium was well grounded.¶ MacCallum, * in a more emphatic way placed the burden of proof on the investigator who designates any tumor as endothelial in origin, yet felt that in certain instances true endotheliomas had been recorded, and he cited such instances.

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‡ Kolaczek: Ueber das Angiosarkom, Deutsche Ztschr f Chir 9 165, 1878

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† Ewing, J A review of classification of bone sarcoma, Arch. Surg. 4 485 (May) 1922.

‡ Ewing, J.: Neoplastic Diseases ed. 3, Philadelphia, Saunders, 1928, p. 351

§ Connor C. L.: Endothelial myeloma, Ewing. Arch. Surg. 12 789, 1926.

‖ Kolodny A.: Bone sarcoma, Surg. Gynec. & Obst. 44 126, 1927

¶ Ewing in his more recent studies does not insist on the endothelial origin of this neoplasm.

MacCallum, W G.: A Textbook of Pathology Philadelphia, Saunders, 1916, p. 928.

ETIOLOGIC FACTORS

Ewing's sarcoma* is a disease of early life 95 per cent of the 167 cases in this series (Table 44) occurred in persons between the ages of 4½ and 25 The youngest person whose case was reported in our series was a child aged 2½, while the oldest was a white man aged 66 (Chart 10) Fifty per cent of the cases were in the decade of 11 to 20 years

Ewing's tumor comprises about 15 per cent of all sarcomas of bone. Males predominate over females in an approximate ratio of two to one. The tumor is apparently rare in all races save the Caucasian only two cases occurred in Negroes 40 per cent of the cases are located in the femur or tibia.

Trauma was recorded in 40 cases, although the actual number in which it occurred was probably greater since in many instances it was not sought for or was not recorded. In every case in which trauma was recorded, it was definitely related to the subsequent onset of the clinical symptoms. The average lapse of time between trauma and symptoms was approximately five and one-half months, the extremes being a few days and more than a year

Etiologically the question arises whether the injury was superimposed on an already existent tumor or whether it was the stimulus for the malignant growth. There are grounds for assuming either conclusion, but the majority of injuries reported probably preceded the disease, but were coincidental.

CLINICAL CHARACTERISTICS

Pain Pain was an outstanding symptom in most cases (80 per cent) and was noted as the first symptom in over 50 per cent. It either began spontaneously followed trauma by a more or less short period, or appeared simultaneously with the formation of tumor

* Codman, E. A. The nomeclature used by the registry of bone sarcoma, Am. J Roentgenol. 13 105 1925

In the majority of cases, pain had bee[n] present for from six weeks to seven month[s] before the patient came under observatio[n] and in twelve cases it had been present fro[m] one to two years prior to clinical observa[-]tion.

A wide variation in the severity of th[e] initial pain was apparent, in some cases [it] was cramplike, while in others it was eithe[r] a sharp shooting pain or an aching on mo[-]tion. Most frequently the pain was inter[-]mittent, lasting from a few hours to severa[l] days, subsiding at intervals, only to recu[r] with increasing severity The intervals be[-]tween the attacks of pain became shorte[r] in duration until a constant discomfort wa[s] noted by the patient. Nocturnal pain wa[s] most severe, in many cases.

The course of the pain may be summe[d] up as follows

Stage 1 Tenderness or soreness follow[-]ing trauma or arising spontaneously on mo[-]tion.

Stage 2 Intermittent pain of a dull ach[-]ing or sharp shooting character lasting from a few hours to several days.

Stage 3 Periods of freedom from pain.

Stage 4 Continuous pain either of a dul[l] aching or sharp shooting nature appearing with progression in the size of the tumo[r] *or spontaneously* and subsiding only afte[r] operative or roentgen treatment.

Tumor In the majority of cases, a mass could be palpated and in 20 per cent a swelling appeared as the initial symptom. The average duration of the tumor before treatment was 13½ months, in the cases seen prior to 1930 In the cases seen from 1930 to 1935 the average is 8 months. One ex[-]ception is of interest, namely a case under observation in which there was a *history* of tumor extending over a period of seven years, the tumor showing many regressions and increases in size before the patient's admission to the hospital.

In only two cases was tumor the only manifestation of the disease. In the major[-]ity of the cases, trauma, pain and tumor or pain and tumor formed the syndrome. In

TABLE 44 EWING'S SARCOMA

Pathologic No	Race	Sex	Age	Location	Duration, mos.	Symptoms	Treatment	Results of Treatment
62394	W	F	2½	Radius	8	Pain	Amputation	Dead 5 wks.
62478	W	M	14	Femur lower	3	Fractures	Irradiation	Dead 3 yr
62528	W	F	14	1st metatarsal	12	Pain		
62278	W	M	14	Humerus	6	Pain	Resected	Well 6 yr
62210	N	F	18	Tibia	4	Tumor	Amputation	Well 6 yr
62174	W	M	12	Humerus, lower	1	Pain	Irradiation	Dead 1 yr
62124	W	F	12	Femur	2		Irradiation	Dead 1 yr
62076	W	F	7	Humerus, lower	18	Pain	Resection, irradiation	Dead 1½ yr
62048	W	F	24	Calcaneus	2½	Pain	Amputation	Dead 1 yr
61914	W	M	13	Pelvis	6	Pain	Irradiation	Dead 1 yr
61768	W	F	33	Scapula	84	Pain	Biopsy	Dead 3 yr
61674	W	M	9	Femur lower	3	Pain	Irradiation, amputation	Dead 4 yr
61568		M	36	Scapula	12	Pain		
60966	W	M	15	Pubis	2		Irradiation	Well 9 yr
60262	W	M	5	Femur lower	5	Pain, tumor	Irradiation	Dead 2 yr
60202	W	F	16	Pubis	5	Pain	Biopsy Irradiation	Dead 1½ yr
60148	W	M	24	Fibula	24	Trauma pain	Irradiation, excision	Dead 1 yr
60094	W	M	22	Great toe	3	Tumor	Amputation	Recurrence 1 yr
59866	W	F	14	Tibia, lower	60	Trauma, tumor		
59786	W	F		Scapula			Irradiation	Dead 2 mos
59464	W	M	10	Tibia, upper	1	Tumor		
59250	W	M	7	Femur midshaft		Pain	Irradiation	
59248	W	F	16	Multiple		Tumor	Irradiation	Lost
59110	W	M	45	Femur lower		Fracture	Exploration	Dead 10 mos.
58826	W	M	14	Femur shaft	60	Pain	Irradiation	
58769	W	M	66	Tarsal bone	3	Pain, tumor	Amputation	
58008	W	M	24	6th rib	8	Tumor trauma	Excision	
57722	W	M	21	Femur upper	12	Tumor	Irradiation, amputation	Dead 6 mos
57718	W	M	4½	Femur upper	¾	Pain	Irradiation	Well 14 yr
57708	W	M	14	Humerus	1	Pain tumor	Amputation	Well 1 yr
57446		F		Tibia			Irradiation	Dead 1 yr
57210	W	M	17	Fibula, upper	3	Pain, tumor	Irradiation	Dead 1½ yr
57176	N	M	21	Radius			Excision, bone graft	Well 12 yr
57163	W	M	9	Ilium	3	Pain	Irradiation	Well 2 yr
56244	W	F	7	Femur	1	Pain		Lost
55722	W	M	12	Humerus	12	Pain fracture	Irradiation	
55068	W	F	7	Fibula, lower	6	Pain	Irradiated	Dead 5 yr
							Irradiation, resection	Well 13 yr

TABLE 45. EWING'S SARCOMA

P N	Race Sex and Age	Location	Duration, mos.	Symptoms	Treatment	Results of Treatment
55606		Rib			Biopsy Aug., 1934 Irradiation	Died Sept., 1935
54606	W F 16	Femur lower	3	Tumor	Biopsy irradiation	Well [illegible] yr
54544	F 10	Femur upper	9	Pain	Irradiation	Lost
54510	W F 11	Femur	12	Pain in knee joint		Well 15 years, 1948
54472	W F 18	Bodies of lumbar vertebra, 4, 5, and 6	6	Pain	Irradiation	Dead [illegible] yr
54352	W M 13	Toe	6	Tumor pain	Leg amputated. Irradiation to metastases	Died in 8 mos. Metastases to lung and vertebra
54144	W M 17	Tibia	22	Pain, limp, tumor	Two biopsies—irradiation	Well 1 yr
53074	W M 14	Femur	7	Tumor	Biopsy irradiation	Well 3 yr
53902	W M 12	Forearm	3	Tumor	Excision	Dead 16 mos.
53878	W M 35	Tibia		Fever pain	Amputation	Well 1 yr
53784	W M 44	Clavicle	18	Tumor	Biopsy resection	Dead 2 yr
53704	W M 44	Clavicle		Trauma, tumor	Deep x-ray therapy	Dead in 1½ yr
53358	N F 3	Femur	1	Tumor	Biopsy irradiation	Dead 1 yr
53320	W F 2	Frontal bone	3	Tumor	Biopsy radium irradiation	Dead 2½ mos.
53201	W F 7	Tibia	1½	Tumor	Biopsy irradiation	Dead 2 yr
52804	W M 10	Femur			Biopsy July 1 1933—irradiation	Well 19 mos.
52910	W M 14	Femur		Tumor pain, limp	Biopsy—irradiation	Dead
52382	W F 17	Humerus	1½	Tumor		
52234	W M 11	Tibia		Pain, tumor	Biopsy Oct., 1933. Irradiation	Dead July 1 1934 Autopsy
51870	W M 11	Rib	3½	Trauma, pain pleural effusion	Biopsy July 1933—irradiation	Died 3 mos. later
51670	W F 7		5	Trauma, pain, tumor	Irradiation	Dead 2 yr
51612	W M 16	Tibia	3	Pain, pathologic fracture	Amputation Oct., 1932	Well 3 years metastasis to pelvis (?)
51566	W F 15	Femur	1½	Trauma pain tumor	Amputation upper third thigh—irradiation	Died in 1 yr metastasis to lungs
51346	W M 32		24	Limp	Irradiation June, 1931	Dead June 6, 1933, [illegible] yrs. later—autopsy
50020	W M 16	Femur	1	Pain, tender	Exploration Mar 10, 1933—irradiation	Dead 6 mos. later Autopsy
49746	W F 23	Spine and pelvis	8	Pain paresthesia	Biopsy Nov., 1932—irradiation	Died July 18, 1933, 9 mos. later—autopsy
49364	W F 8	Tibia			Irradiation—amputation	Died in 3 mos. metastasis to skull—autopsy

40072	W	M	5	Mastoid		Pain	Polyp removed from ear—recurred in one week	Dead in two mos.
48886		M		Os Calcis			Surgery	Dead 5 yr
48814	W	M	30	Rib	6	Tumor cough, pleurisy	Biopsy—irradiation	Died within 2 yr
48906	W	M	5	Scapula	1		Irradiation	Well 1 yr Lost
48780	W	M	10			Trauma, pain, limp, tumor	Irradiation April, 1931	Died Jan. 7 1932, metastasis head and chest. Autopsy
48686	W	M	25	Tibia			Amputation—irradiation	Died in 7 mos.
48174	W	F	10	Femur			July 1932 amputation	Died July 1933. Pulmonary metastases
48282	W	F	10	Femur		Pain	Irradiation advised	Lost
47926	W	F	15	Femur	10	Pain trauma, fracture	Jan. 7 1932, biopsy—irradiation	Died in 6 mos.
47032	W	M	17	Femur	5	Pain, limp	Exploration—irradiation	Died in 13 mos.
46922	W	F	8	Humerus			Irradiation—resection	Well 4 yr
46890	W	M	15	Femur	2	Pain, limp, tumor	Irradiation	Died in 4 mos.
40796	W	M	3	Jaw tibia, femur	1	Tumor pain	Biopsy jaw Oct., 1931 Radium Oct. 23, 1931	Died Dec. 31 1931
46820	W	M	20	Humerus	2	Pain	Resection—irradiation	Died in 8 mos. metastasis to lungs
40140	W	M	37	Tibia	12	Trauma, pain, tumor	Biopsy Sept. 11 1931	Lost
45530	W	M	8	Humerus	1½	Trauma, tumor	Biopsy Aug. 14, 1931	Dead in 4 mos.
45826	W	M	21	Femur	12	Pain, tender	Curettement July 1931 radium	Dead July 1932
45202	W	F	25	Fibula	24	Pain	Biopsy irradiation	Dead 3 yr
44702	W	M	60	Humerus	1	Pain	Amputation	Dead 1 yr
44721	W	M	20	Tibia	3	Trauma tumor pain	Irradiation Mar 30, 1931	Died May 18, 1932, metastasis to lungs
44490	W	F	17	Ilium	36–48	Pain, limp	Exploration—curettage Dec. 23, 1930	Died 10 mos. after operation
44308	W	M	10	Humerus	9	Pain	Resection	Dead 14 yr
44204	W	M	5	Foot	18	Intermittent tumor	Curettement—irradiation	Died in 1½ yr after operation
44088	W	M	10	Ilium	3	Trauma, pain	Irradiation Nov 17 1930	Died June 15, 1931 metastasis to skull
44024	W	M	7½	Clavicle	24	Tumor	Irradiation	Lost
44016	W	M	22	Rib	12	Pain	Exploration—curettage—irradiation advised	Died in 3 yr metastasis to skull and pelvis
43906	W	M	18	Ischium	7	Pain tumor	Excision	Dead 1 yr

TABLE 48. EWING'S SARCOMA

P N	Race Sex and Age	Location	Duration, mos.	Symptoms	Treatment	Results of Treatment
55006		Rib			Biopsy Aug 1934 Irradiation	Died Sept., 1935
51606	W F 16	Femur lower	3	Tumor	Biopsy irradiation	Well 2 yr
51511	F 10	Femur upper	0	Pain	Irradiation	Lost
51510	W F 11	Femur	[illegible]	Pain in knee joint		Well 15 years, 1918
51172	W F 18	Bodies of lumbar vertebra, 4 5, and 6	6	Pain	Irradiation	Dead 3 yr
51352	W M 13	Toe	6	Tumor pain	Leg amputated . Irradiation to metastases	Died in 8 mos. Metastases to lung and vertebra
51144	W M 17	Tibia	22	Pain, limp, tumor	Two biopsies—irradiation	Well 1 yr
53971	W M 11	Femur	7	Tumor	Biopsy irradiation	Well 3 yr
53002	W M 12	Forearm	3	Tumor	Excision	Dead [illegible] mos.
53378	W M 35	Tibia		Fever pain	Amputation	Well 1 yr
53781	W M 41	Clavicle	18	Tumor	Biopsy resection	Dead 2 yr
53701	W M 44	Clavicle		Trauma, tumor	Deep x ray therapy	Dead in 1½ yr
53368	W F 3	Femur	1	Tumor	Biopsy irradiation	Dead 1 yr
53320	W F 2	Frontal bone	3	Tumor	Biopsy radium irradiation	Dead 3½ mos.
53201	W F 7	Tibia	1½	Tumor	Biopsy irradiation	Dead 2 yr
52891	W M 10	Femur			Biopsy July 1 1933—irradiation	Well 19 mos.
52910	W M 14	Femur		Tumor pain, limp	Biopsy—irradiation	Dead
52582	W F 17	Humerus	1½	Tumor		
52231	W M 11	Tibia		Pain, tumor	Biopsy Oct., 1933. Irradiation	Dead July 1 1934 Autopsy
51970	W M 11	Rib	3½	Trauma, pain, pleural effusion	Biopsy July 1933—irradiation	Died 3 mos. later
51670	W F 7		5	Trauma, pain, tumor	Irradiation	Dead 2 yr
51612	W M 10	Tibia	3	Pain, pathologic fracture	Amputation Oct., 1932	Well 3 years metastasis to pelvis (?)
51560	W F 15	Femur	1½	Trauma, pain, tumor	Amputation upper third thigh—irradiation	Died in 1 yr metastasis to lungs
51346	W M 32		[illegible]	Limp	Irradiation June 1931	Dead June 6, 1933, 2 yrs. later—autopsy
50020	W M 10	Femur	1	Pain, tender	Exploration Mar 10, 1933—irradiation	Dead 6 mos. later Autopsy
49746	W F 23	Spine and pelvis	8	Pain paresthesia	Biopsy Nov., 1932—irradiation	Died July 18, 1933, 9 mos. later—autopsy
49304	W F 8	Tibia			Irradiation—amputation	Died in 3 mos. metastasis to skull—autopsy

No.	Race	Sex	Age	Site	Duration	Symptoms	Treatment	Result
40072	W	M	5	*Mastoid*		Pain	Polyp removed from ear—*recurred in one week*	Dead in two mos.
48886		M		Os Calcis			Surgery	*Dead 5 yr*
48844	W	M	30	Rib	6	Tumor cough, pleurisy	Biopsy—irradiation	Died within 2 yr
48306	W	M	5	*Scapula*	1		Irradiation	Well 1 yr Lost
48780	W	M	10			Trauma, pain limp, tumor	Irradiation April 1931	Died Jan. 7 1932, metastases head *and chest.* Autopsy
48696	W	M	23	Tibia			*Amputation—irradiation*	Died in 7 mos.
48424	W	F	*10*	*Femur*			July 1932 amputation	Died July 1933. *Pulmonary metastases*
48282	W	F	10	Femur		Pain	Irradiation advised	Lost
47926	W	F	15	Femur	10	Pain trauma, fracture	Jan 7 1932, biopsy—irradiation	Died *in 6 mos.*
47032	W	M	17	Femur	5	*Pain, limp*	Exploration—irradiation	Died in 13 mos.
46922	W	F	8	Humerus			Irradiation—resection	Well 4 yr
46800	W	M	15	Femur	2	Pain limp, tumor	Irradiation	Died in 1 mos.
40796	W	M	3	Jaw tibia, *femur*	1	Tumor pain	Biopsy jaw Oct., 1931 Radium Oct. 23, 1931	Died *Dec 31* 1931
46020	W	M	[illegible]	Humerus	2	Pain	Resection—irradiation	Died in 8 mos. metastasis to *lungs*
46140	W	M	37	Tibia	12	Trauma, pain tumor	Biopsy Sept. 11 1931	*Lost*
45830	W	M	8	Humerus	1¼	Trauma, tumor	Biopsy Aug. 14 1931	Died in 4 mos.
45820	W	M	21	Femur	12	Pain, tender	Curettement July 1931 *radium*	Dead July 1932
45202	W	F	25	Fibula	24	Pain	Biopsy irradiation	Dead 3 yr
44702	W	M	[illegible]	*Humerus*	4	Pain	Amputation	*Dead 1 yr*
44724	W	M	[illegible]	Tibia	3	Trauma tumor pain	Irradiation *Mar* 30, 1931	Died May 18, 1932, metastasis to lungs
44480	W	F	17	Ilium	36–48	Pain, limp	Exploration—curettage Dec. 23, 1930	Died 10 mos. after operation
44368	W	M	10	Humerus	2	Pain	Resection	Dead 11 yr
44264	W	M	5	*Foot*	18	Intermittent tumor	Curettement—irradiation	*Died in 1¼ yr* after operation
44088	W	M	16	Ilium	3	*Trauma, pain*	Irradiation Nov 17 1930	Died June 13, 1931 metastasis to skull
44024	W	M	7½	Clavicle	24	Tumor	*Irradiation*	Lost
44016	W	M	[illegible]	Rib	12	Pain	Exploration—curettage—irradiation advised	Died in 3 yr metastasis to skull and pelvis
43900	W	M	18	Ischium	7	*Pain, tumor*	Excision	Dead 1 yr

TABLE 15. EWING'S SARCOMA (*Continued*)

P. N.	Race, Sex and Age	Location	Duration, mos.	Symptoms	Treatment	Result of Treatment
43306	W M 18	Ischium	7	Trauma, pain	Biopsy Oct. 18, 1930—irradiation	Died in 13 mos
43798	W M 17	Femur	10	Pain, tumor	Irradiation	Died in 3 yr metastasis to vertebra
43009	W F 21	Humerus	6		Resection	Died in 1 yr metastasis to lungs
43308	W F 7	Femur	9	Pain tumor	Biopsy—excision ; Radium June 20, 1929	Dead Jan 1931 Recurrence and metastases to lungs
43250	W M 17	Femur upper			Amputation, July 11 1930	Dead
42302	W F 11	Pubis	10	Trauma, tumor	Incision July 26, 1929 x-ray	Metastases to bone; dead 8 mos later
42220	W F 14	Os calcis	24	Pain, limp, tumor	Incision Sept. 25, 1929 and drainage biopsy Oct. 14 1929; amputation Nov 12, 1929 irradiation	Dead 6 mos after amputation
42010	W F 24	Phalanx, distal, thumb	1	Pain	X-ray Aug 20, 1929 resection Aug 20 1929	Well 11½ mos. after operation
40530	W M 14	Tibia, lower ⅓ shaft	4	Trauma, pain	Exploration, Apr 1928 amputation May 23, 1928	Dead 6 mos. after amputation
40312	W M 27	Ribs	3	Difficulty in breathing following trauma tumor	Irradiation, following two aspirations, early in 1927	Dead
40026	W F 9	Ilium, right	[illegible]	Trauma, pain	Irradiation, excision of metastatic tumor distal phalanx of toe	Dead [illegible] mos. after operation
39868	W F 7	Fibula	9	Pain	Irradiation	Dead 3 yr
30716	W F 11	Os calcis	6	Pain	Resection	Dead 1 yr
37472	W M 28	Humerus, lower shaft and epiphysis	120	Pain; tumor three years	Resection Jan 18, 1926 bone transplantation May 10 1926	Dead 5 yr., after operation
36412	W M 18	Tibia	12	Tumor	Amputation	Dead 1 yr
33332	W F 8	Tibia shaft	6	Pain, tumor limp	Amputation, Oct. 7 1924	Dead 1 yr 10 mos., after amputation
35706	W F 16	Rib, 4th	1½	Pain, tumor	Excision, Sept. 4 1924 exploration and excision Jan. 21 1926	Dead a few months after operation
35654	W M 21	Tibia, upper shaft	50	Trauma, tumor	Amputation Sept. 20, 1924	Dead 4 mos. after amputation

35014	W F 22	Tibia lower shaft	48	Trauma, tumor pain	Curettement, Feb. 3, 1921 P O irradiation	Well 10 yr., after operation
34422	W M 10	Fibula, upper shaft	4	Trauma, tumor limp	Amputation Dec., 1923	Dead 4 yr 1 mos., after amputation
34344	W F 17	Femur lower shaft	5	Pain, tumor	† Pre-op irradiation	Dead 1 yr., 8 mos. after appearance of symptoms
34027	W M 23	Ilium	11	Trauma, pain, tumor	Exploration	Dead 11 mos. after trauma
34005	W M 19	Humerus, lower	84	Tumor (recurrent) pain	Resection, Oct. 12, 1923	Well over 2 yr., lost
33807	W F 22	Mastoid	4	Pain, tumor	Mastoidectomy Aug 2, 1922 excision Nov 18, 1922	Dead 7 mos. after 1st operation, autopsy
33801	W M 21	Fibula	6	Tumor	Amputation	Dead 1 yr
32910	W M 17	Tibia, shaft	[illegible]	Pain, tumor	Exploration July 1920 P O radium and x-ray	Dead 3 yr., 4 mos., later
32770	W M 7½	Tibia, shaft	18	Tumor	Excision Apr 27 1923 P O x-ray	Dead 16 mos. after operation
32823	W M 11	Radius, shaft	5	Tumor	Exploration amputation, Mar 9 1923 P O x-ray	Dead 17 mos. after operation
32174	W M 16	Femur lower shaft	6	Trauma, tumor slight pain	Amputation Jan., 1923	Dead 6 mos. later
31988	W M 17	Femur upper	2	Pain, tumor	Exploration, Dec 23, 1922 P O radium and x-ray	Dead 3 yr., 3 mos., after operation
31175	W M 22	Fibula, shaft		Pain, swelling (intermittent)	Exploration, twice curettement resection Sept., 1922 P O x-ray and radium	Dead 3 mos. after resection
30944	W M 20	Tibia, lower shaft	7	Tumor slight pain	Pre-op. irradiation, Aug. 6, 1922	Dead almost 6 mos. after treatment
30919	W M 32	Ulna	0	Trauma, tumor	Amputation, Oct 28, 1922	Dead from operation
30828	W F 9	Humerus, upper shaft	12	Tumor	Exploration, Aug 1 1922	Dead less than 1 yr after operation

P O = post-operative † Pre.-op = preoperative

TABLE 45 EWING'S SARCOMA (*Continued*)

P N	Race Sex and Age	Location	Duration, mos	Symptoms	Treatment	Results of Treatment
30733	W M 12	Fibula, upper shaft	2	Pain tumor	Coley's Serum and radium, Aug 26, 1921	Dead 10 mos. later
30194	N F [illegible]	Femur upper shaft	[illegible]	Tumor	Irradiation Coley's serum	Dead
30072	W F 31	Ilium	5	Pain, tumor	Exploration, Feb 18, 1922	Dead 11 mos. after operation
29296	W F 12	Tibia, upper shaft	12	Pain, tumor	Exploration amputation, Mar 1921	Well 6 yr., 6 mos., after operation
29034	W M 7	Tibia, shaft			Curettement, Dec., 1919 curettement cauterization, Oct. 4 1921	Dead 1 yr later after 2d operation
28835	W M 24	Femur lower shaft	4½	Pain, tumor	Amputation, Sept 16, 1921	Died 4½ mos. after operation
28[illegible]4	W F 34	Ilium, sacroiliac joint	5	Pain	Exploration Sept. 8, 1921	Dead 1 day after operation
28600	W M 11	Humerus, upper shaft	1½	Pain, tumor	Amputation, Mar 11 1921 P O Irradiation	Dead 6 mos. after operation
28307	W F 12	Humerus, upper shaft		Tumor pathological fracture	Exploration, April, 1920 amputation May 1920	Well nearly six yr after amputation
28303	W M [illegible]	Fibula, lower shaft	9	Trauma, pain, tumor	Exploration resection, Oct., 1916	Dead 1 mo. later
28364	W M [illegible]	Fibula, upper	[illegible]	Trauma, pain, tumor	Amputation Jan 13, 1921	Dead 8 mos. after operation, metastasis to skull
27631	W F	Scapula, clavicle		Pain tumor	Excision scapula and outer end of clavicle, June, 1920 excision clavicle, Sept. [illegible] 1921 P O Irradiation	Well almost 9 yr later
27511	W M 14	Femur lower	6	Trauma, pain tumor	Amputation, Jan. 8, 1921	Dead 5 mos. after operation
27039	W M 9	Scapula	6	Pain, tumor	Pre-op Irradiation resection Sept. 10, 1922	Dead 9 mos. after operation

26016	W M 23	Femur lower shaft	11	Trauma, pain tumor	Amputation Nov., 1920 higher amputation, Nov., 1921 P O x-ray	Dead within 1 mo after 2d amputation
26915	W M 16	Phalanx proximal, great toe			Amputation toe amputation leg twice	Dead over 3 yr after 1st amputation
26901	W M 13	Clavicle			Resection Mar 28, 1919 excision recurrence June 1920 P O x-ray	*Well 7 yr., 3 mos.*, after 2d operation
26885	W F 44	Tibia, upper	4	Pain tumor	Amputation 1922	Dead within 1 yr after operation
26507	W M 30	Os calcis	24	Pain, tumor	Amputation Aug. 13, 1920	Dead 3 mos. after amputation
25906	W F 19	Scapula	24	Trauma, pain, *tumor*	Partial resection, April 10, 1920 radium	Dead 1 yr., 2 mos., after operation
25430	W F 10	Fibula, shaft	12	Pain tumor	Excision, Dec 11 1919 excision, Aug 2, 1920 radium	Dead 10 mos. after 2d operation
24927	W M 6	Tibia, shaft	18	Trauma, pain, tumor	Exploration and amputation Aug 20, 1919	Dead 1 yr., 1 mo later
24667	W M 11	Femur upper shaft	14	Pain, tumor	Excision Nov 18, 1918 amputation July 1919 after x-ray and Coley's Serum	Dead 16 mos. after 2d operation
23984	W M 15	Tibia, upper	12	Pain, tumor	Exploration and amputation, Dec. 14 1918	Dead 1 yr., 4 mos., after operation
22795	W M 22	Femur lower shaft	24	Pain, tumor	Amputation Jan 8 1918	Well 12 yr., 7 mos., later
20700	W M 24	Fibula, lower	1	Trauma, pain tumor	Exploration, Jan 18, 1916 excision Mar 8, 1916 amputation, Mar., 1916	Dead a few months later
15921	W F	Pelvis		Trauma, pain, tumor	Exploration, June 19, 1914 attempted excision June 30, 1914 2d attempted excision, July 3, 1914	Dead from last operation

TABLE 45. EWING'S SARCOMA (*Continued*)

P N	Race Sex and Age	Location	Duration mos	Symptoms	Treatment	Results of Treatment
15745	W F 14	Femur upper	[illegible]	Pain tumor	Exploration, May 15 1914	Dead 3½ mos. after operation
13439	W M [illegible]	Humerus, upper	5	Trauma, pain	Excision gland, Dec. 9 1912 Coley's Serum	Dead 2 mos. after operation
11444	W F 9	Metatarsal	6	Tumor	Excision	Dead (?) Lost
10637	W M 17	Tibia, upper	6	Pain tumor	Excision, partial, April 29, 1910 Coley's Serum	Dead 6 mos. after operation
8509	W F 4½	Scapula	2	Trauma, tumor	Amputation, Oct. 7 1907	Lost
8090	W M 20	Ilium	9	Trauma, pain, tumor	Exploration, Apr 6, 1907	Lost
7963	W M 13	Fibula, shaft	12	Pain, tumor	Amputation, Jan 16, 1904	Dead 4 mos after operation
7657	W M 16	Fibula, shaft	6	Trauma, pain, tumor	Exploration and excision, Nov., 1906	Dead 11 mos. after operation
5927	W M 7	Femur lower	2½	Pain, tumor	Excision, Sept. 21 1903 Irradiation excision small piece of recurrence, Dec. 9, 1903	Dead less than 1 mo after last operation
5172	W F 11	Tibia, shaft		Trauma, pain, tumor	Incision amputation, Nov 24, 1903	Dead 2 mos after amputation
4392	W F 17	Humerus, upper shaft	3	Pain, tumor	Incision, amputation and excision axillary glands, Aug. 22, 1902	Dead 11 mos. after amputation
3009	W M 24	Femur upper	36	Fracture (non-union) pain and tumor	Exploration 1899 amputation, Mar 24, 1900	Dead 2 yr., 2 mos., after amputation
1207	W F 8	Tibia, upper	9	Trauma, pain, tumor	Amputation, Jan. 17 1896	Dead 10 mos. after amputation
64	W M [illegible]	Humerus, upper shaft	6	Pain, trauma, tumor	Amputation, Nov 3, 1892 and excision axillary glands	Dead 5 mos. after operation

many cases, the tumor was preceded by pain or trauma for a period ranging from two months to one year about the growth, in many cases. The soft parts about the tumor were freely movable, but often were edematous, while in other

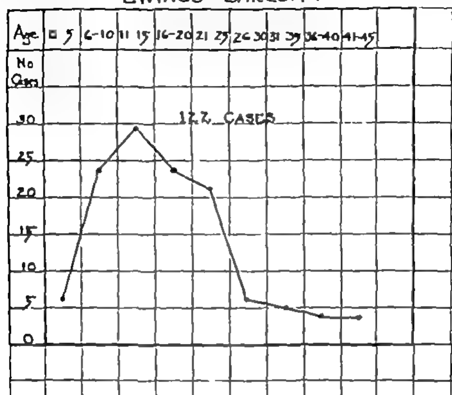


CHART 10 Age incidence of Ewing's sarcoma.

TABLE 46 BONY INVOLVEMENT IN EWING'S SARCOMA

Bone Involved	Total Number of Cases	Cases in Upper Shaft	Cases in Lower Shaft	Cases in Mid-shaft
Femur	28	15	7	6
Tibia	24	9	3	12
Jaw	16			
Humerus	12	2	1	2
Pelvis	12			
Fibula	10	4	2	4
Scapula	8			
Ribs	5			
Skull	2			
Os calcis	2			
Clavicle	2			
Metatarsal	2			
Radius	1		1	
Tarsal	1			
Vertebra	1			

The mass varied from a small localized swelling to a large fusiform one extending along almost the entire length of the affected bone. There were vasomotor changes cases there was only dilatation of the superficial veins. In many instances a local elevation of the temperature was noted.

Palpation disclosed an indurated swell



Fig. 281 Roentgenograms of Ewing's sarcoma, showing the characteristic onion-peel appearance of the periosteal reaction and the extension of the tumor along the shaft. *(Top)* (No 28835) Roentgenogram of Ewing's sarcoma of the lower humerus. *(Bottom)* Roentgenogram of Ewing's sarcoma involving the ramus of the pubic bone. The roentgenogram of the pubic bone is characteristic.

ing, irregular or smooth, and often fixed or apparently continuous with the bone. Fluctuation was not noted, though there were varying degrees of resilience, all being less hard than bone. Many of the tumors were tender

A peculiar feature in some of the tumors was their tendency spontaneously to decrease in size, with a sudden cessation of pain, and thus to disappear and reappear until some treatment was instituted. Perhaps the variability in the size of the tumor from time to time had to do with hemorrhage and its absorption.

The bones most frequently involved were the long pipe bones (Table 46) although in a few instances the ilium, scapula, clavicle, vertebra, skull and bones of the feet were affected (Fig 282) In no case was the primary location in other than the shaft, where the long bones were involved.

Pathologic fracture was relatively rare. *It was noted in only five cases of this series.* These fractures were of the femur two occurring in the upper shaft and one in the lower shaft and two in the upper humerus. The infrequency of pathologic fracture* in this round-cell sarcoma is against the current opinion that this tumor is a primarily bone-destructive neoplasm, although pain of the affected part (due to weight bearing) may in some instances, have saved the limb from this complication.

Constitutional Reaction The temperature was adequately recorded in 70 cases. The range of the elevation of temperature was between 99 and 104° F., the average being 100. These elevations of temperature were more commonly observed late in the disease, after metastases had occurred, but fever was noted early in the clinical course in 30 per cent of the cases. Associated with this fever in many cases, were slight albuminuria and a few white and red blood cells in the urine. Though a search for Bence-

* Geschickter C. F., and Copeland, M. M.: Multiple myeloma, Arch. Surg. 16 807 1928 Osteitis fibrosa and giant-cell tumor ibid. 19 161 201 1929.

Jones bodies was apparently not a routine procedure in the cases in which the test was carried out, they were not found in a single instance

In cases in which the blood was examined in detail the picture ranged from normal to a secondary anemia and from leukopenia to marked leukocytosis. Of 50 cases 5 presented red-cell counts of 5 000 000 or more and an equal number red-cell counts of 4,000 000 or more The remaining cases showed red-cell counts ranging between 2, 900,000 and 3 900 000 No case showed anemia of the primary type or severe secondary anemia. The hemoglobin in these cases ranged between 50 and 90 per cent.

Of the cases in which the white-cell count was recorded, 10 had counts, within normal limits 40 had counts of more than 10,000 3 being more than 20 000 There were no unusual features in the differential counts, save an occasional eosinophilia ranging from 4 to 20 per cent. Myelocytes were not noted for any increase in the number of the mononuclear elements. Leukocytosis was not restricted to cases with metastases but was often an initial observation early in the course of the disease In suspected cases of Ewing's sarcoma with a relative lymphocytosis, involvement of several bones suggests lymphatic leukemia.

Of interest is the great variability in the nutrition of the patients suffering from Ewing's sarcoma. In some cases a noticeable loss of weight over a relatively short period of time was observed early in the course of the disease while in other cases little or no evidence of undernutrition was seen until the end. The terminal phases, however revealed progressive emaciation

Internal metastases occurred late in the disease. In many cases, there were pains in the chest, hemoptysis and other clinical manifestations of pulmonary disease. In no case were the changes in the lungs due to changes in body stance, as often occurs in multiple myeloma. Vertebral metastases, when they occurred, were occasionally accompanied by paraplegia. In one patient showing choked disks and retinitis, blindness developed, but this was produced by metastatic involvement of the cranial vault with protrusion into the cranial cavity rather than by direct involvement of the

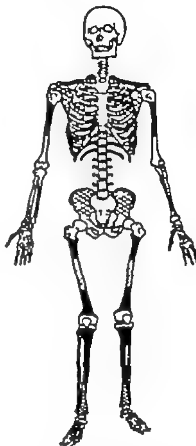


FIG. 282. Incidence of Ewing's sarcoma according to skeletal location. The solid black areas indicate the most frequent sites the checked areas, the common sites; the diagonal lines, the occasional sites and the dotted areas, rare sites. The areas in white were not involved by tumor in this series.

brain substance. Not infrequently with metastases to the skull and vertebrae, evidence of motor irritation was noted. In these cases of bone metastases, particularly in young individuals, it is difficult to rule out the possibility of neuroblastoma arising in the adrenal medulla. The undifferentiated neuroblastoma of the adrenal and Ewing's



Fig. 283 (No 35882) (A) is a roentgenogram of a tibia made six months after the onset of symptoms. It shows a slight shadow in the midshaft region of the bone and a slight widening of the cortex, with little if any periosteal reaction. (B) was made eleven days later It shows increased density of the tumor shadow and a definite periosteal reaction. The normal tibia is included in (B) for contrast



Fig. 284 (No. 31241) Ewing's sarcoma in an early stage. There is relatively little medullary involvement, a slight expansion of the shaft and thickening of the cortex. There is a action, looking somewhat like onion peel.



FIG. 283 (No. 48780) Ewing's sarcoma involving the shaft of a femur One may observe the metaphyseal location of the tumor and its extension along the shaft.

sarcoma resemble each other histologically and both are radiosensitive lesions.

ROENTGEN STUDIES

Ewing's sarcoma as seen roentgenographically is most often situated near the midshaft region of a long bone. Increased density of bone, which reacts vigorously to tumor invasion in the subperiosteal and the endosteal regions, may be the initial change observed. In one case of this series (Fig. 283A) a roentgenogram was made six months after the onset of symptoms. When studied, it revealed increased density in the midshaft region of the bone and a widened but apparently well preserved cortex with little or no periosteal reaction. A roentgenogram (Fig 283B) made eleven days later revealed a fully developed Ewing's sarcoma, with a greater and denser tumor shadow in the midshaft region and definite periosteal reaction.

Roentgenograms have been studied in more than 100 cases Of this number 25 represented early stages with relatively little medullary involvement, the duration of symptoms having been from two to seven months (Fig 284) The roentgenograms in these cases showed a slight expansion of the shaft with a periosteal reaction looking somewhat like onion peel The cortex appeared thickened with some mottling in the region of the medullary cavity The roentgenograms in the other cases, made later in the course of the disease showed a considerable part of the shaft affected apparently the tumor extended more readily in a plane parallel to the axis of the bone.



FIG. 286 (No. 22795) A roentgenogram of Ewing's sarcoma showing osteophytes at right angles to the cortex, together with a thickening of the cortical bone This reaction is metaphyseal and diaphyseal.

In these areas, the medullary cavity often showed osteoporosis and the cortex, bone destruction (Fig. 285) In all of the cases in this group there were varying degrees of periosteal reaction besides invasion of the marrow cavity but increased density



FIG. 287 (No 34005) Involvement of the epiphysis by Ewing's sarcoma. This was subsequently proved to be a secondary invasion, the original tumor having arisen in the shaft of the bone. Osteophytes may be seen arranged perpendicularly to the cortex, with considerable destruction of cortical bone.

in the region of the widened cortex was the most characteristic evidence of infiltration by the tumor

Osteophytes, arranged irregularly or at right angles to the cortex (Fig 286) repeatedly appeared in the pictures, presenting the so-called "groomed whiskers" effect. An investigation into the nature of these osteophytes is of interest and will be presented later The perpendicular spicules of bone in Ewing's sarcoma are produced by a disturbance in the relation of the periosteum to the cortex.

In only three cases did the roentgenogram reveal involvement of the epiphysis (Fig 287) and in these the epiphyses were secondarily invaded, the original tumor having arisen in the shaft of the bone. When the tumor invaded the muscles, the soft part shadow was often well circumscribed.

The roentgen observations may be summarized thus Ewing's sarcoma expands the shaft of long bones by a diffuse infiltration, which results in widening and increased density of the cortex and a mottling of the marrow cavity Both formation and destruction of bone are secondary to infiltration by tumor In the early stage, formation of bone predominates, giving rise eventually to either parallel or radiating periosteal spicules. In the later stages, destruction of bone, both medullary and cortical, characterizes the roentgenogram.

The roentgen studies do not support the view that Ewing's tumor is primarily destructive, for in 25 early cases the first evidence of infiltration by the tumor was an increase in the density of the bone. In two

other recent cases involving the os calcis and vertebra respectively the only evidence of tumor involvement shown in the roent genogram was a marked sclerosis of the bone (Fig 300) The typical contour of this, the infiltration by the Ewing tumor is generally elliptical, with its long axis par allel to the shaft of the bone, indicating that the growth is resisted in the opposite direc tions extending more readily up and down

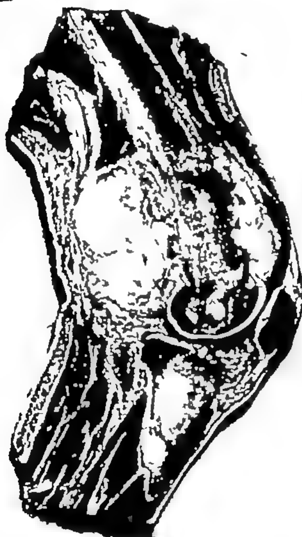


Fig 288 (No. 26916) A gross specimen in longitudinal section showing the primary involve ment of the shaft with a secondary invasion of the epiphysis. The bulk of the tumor is beneath the periosteum and outside the cortical region. The tumor appears well encapsulated.

the part involved speaks against the cur rent conception of the medullary origin of this neoplasm. Medullary tumors should show an approximately spherical shape in early cases, because their expansion is un hindered in all directions. In contrast to

GROSS SPECIMENS

An analysis of the pathologic changes in Ewing s tumor made from gross specimens aided materially in the interpretation of the roentgenograms. The location was usually the shaft of a long bone, and the tumor ex

tended from the midshaft region to the epi physis, the epiphysis being secondarily involved (Fig 288) in but three instances. Regardless of the origin, all the gross speci mens with one exception showed the bulk of the tumor lying subperiosteally (Fig 288) The medullary cavity sometimes con tained a small portion of the tumor but usually this region was narrowed or totally occluded by new reactive bone (Fig 289) The widened cortex described in the roent genogram was shown in the gross speci mens to be made up of subperiosteal and endosteal new bone, which encroached on the medullary space and frequently sealed it off from invasion by the tumor

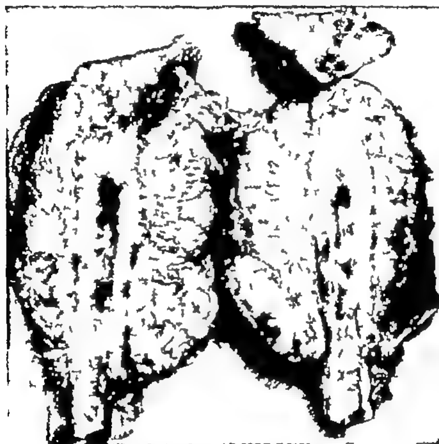


FIG. 289 (No. 37472) A gross specimen of a humerus in lon gitudinal section. The widened cortex described in the roentgeno-gram is shown, in the gross specimen, to be made up of subperi osteal and endosteal formation of new bone, which encroaches on the medullary space.

Although in one case the shaft of the bone surrounded by tumor was almost destroyed, in the majority of the specimens destruction was not a prominent feature. The tumor in its early stages appeared to infiltrate rather than to destroy bone, and the bone thus infiltrated reacted vigorously with ossification But the bone subsequently did undergo destruction when surrounded and infiltrated by the tumor apparently as the result of interruption of the blood supply where the tumor had invaded and blocked the Volkmann and haversian canals.

When the involvement was diffuse, the subperiosteal formation of new bone was both parallel and at right angles to the cortex (Fig. 283) As was pointed out by Buerger* in a case of "dissolutive" sarcoma, this normal formation of new bone was

* Buerger L.: Bone sarcoma, Surg. Gynec. & Obst. 9 441, 1909. Further studies of sarcoma of bone, Am. J M. Sc. 140: 833, 1910.

fairly striking in various parts of the tumor The origin of this bone is explained by the mode of advance of the neoplasm Because of the growth of the tumor and subsequent hemorrhage, there is a gradual separation spicules of new bone from the subperiosteal region are laid down at right angles to the shaft rather than parallel (Fig. 290) We agree with Ribbert that this is due to the blood vessels perforating Volkmann's ca

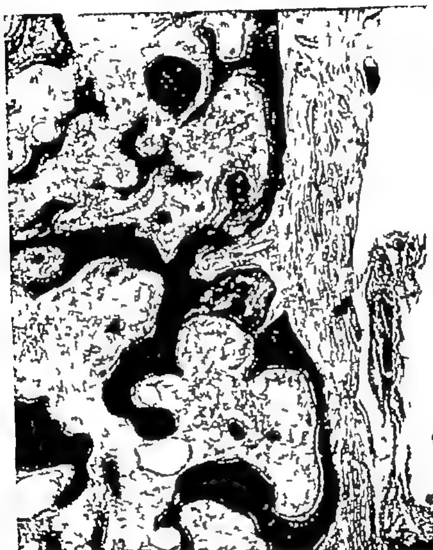


FIG. 290 (No 34005) A photomicrograph showing the periosteum with its subperiosteal layer forming spicules of reactive bone peripheral to the invasion by tumor One may note osteoblasts about the spicules of bone These spicules constitute the right-angle formations of bone seen in the roentgenograms.

of the periosteum from the underlying cortex. Parallel deposits of new bone appear as a result of proliferation of the peripheral layer of the cortex when the periosteum has suffered minute separation. This gives the onion peel like formation characteristic in roentgenograms of the early stages. With increased separation of the periosteum, nals.* After separation of the periosteum these vessels determine the direction of the new growth of bone when they are pulled outward in maintaining their continuity The two types of formation of bone, parallel and radiating, duplicate the process ob-

* Stöhr P Textbook of Histology Philadelphia, Blakiston, 1903, p. 151.

served in the embryo. The bone laid down parallel to the shaft is the first to appear in the tumor and also in the embryo In the first two months of life, osteoblasts about budding vessels lay down osteoid tissue parallel to these channels and form the inteal vessels forms the Volkmann s canals seen in the mature bone, which unite the periosteal vessels with the haversian system. This determination of the pattern of the bone by vessel units typical of the embryo is not lost in the adult.

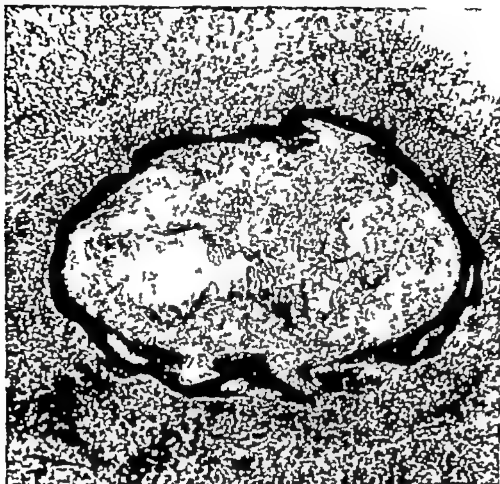


FIG. 291 A photomicrograph of a cross section, from the humerus of a human embryo 90 mm long One may note the enclosure of vessels by osteoid tissue in the cortical region The vessels remain as units in the future haversian systems. The cartilage in the center of the bone is being gradually destroyed and replaced by marrow elements

ner part of the future cortex, the vessels remaining as units in the future haversian system (Fig. 291)

About the second month of embryonic life, this thin osteoid rim of bone is perforated by vessels from the fetal periosteum.* giant cells preceding the vessels (Fig 291) The reformation of bone about these perios

The soft part tumor was usually encapsulated by a thin layer of fibrous tissue, which at its margin was continuous with the periosteum. The tumor itself enclosed by this capsule, was firm and grayish-white and was divided into characteristic lobules by a number of connective tissue strands extending from the outer capsule to the region of the cortical bone. Occasionally the tumor substance showed cysts (Fig 293) filled

* Ewing, E. H. Bone formation in osteogenic sarcoma, Arch. Surg. 12 867 1926

with a dark, pigmented, jellylike material These cysts were due to hemorrhage or regressive changes, for many of the specimens showed soft necrotic areas honeycombing their structure

cell was altered The nucleus was deeply stained, showing a definitely limiting membrane and a sparse scattering of chromatin granules without any definite arrangement Nucleoli were rarely seen but mi



FIG. 292. A B (No. 52234) Ewing's sarcoma of the right tibia in a boy aged 11 with skull metastases three months after biopsy and irradiation. (A) Tibia after exploration. (B) Skull three months later

totic figures were noted not infrequently The diameters of the nuclei ranged from 7 to 9 microns. Little pleomorphism was observed, and multinucleated cells of tumor origin were not noted. Not infrequently however osteoclasts were located in the region of dead bone or a slight distance from the bony tissue in the midst of tumor cells.

There appeared to be no intercellular stroma, but a fibrous trabeculation with a hyaline-staining intercellular substance divided the tumor tissue into lobules where it infiltrated the soft parts. These septa often gave the tumor an alveolar appearance (Fig. 296)

Vascularity was a variable feature of these tumors in some it was mar

MICROSCOPIC OBSERVATIONS

The microscopic characteristics of Ewing's tumor are among the most uniform of the disease. Examination of sections from these tumors without consideration of special areas revealed a more or less constant picture. The type of cell in the compact areas was small and polyhedral with a round or oval nucleus (Fig 294) The cytoplasm was scanty and practically stainless.

In less compact regions, the cells showed a cytoplasm with a more definite outline, which surrounded the nucleus with a pale-eosin staining substance the periphery of which was irregular (Fig. 295) The cells were at times so closely packed that the shape of the individual

F

297) In certain sections, haversian canals, occupied by blood vessels, were secondarily infiltrated by tumor cells (Fig. 298) In these localities, the tumor cells were *sometimes within and sometimes without* the vessel walls. Phenomena of this character have been cited by some authors as evidence of the seat of origin of Ewing's sarcoma. We are inclined to the belief however that, in most of these instances, tumor cells were traversing the haversian system, following the path of least resistance *in their invasion* of bone.



Fig. 293 (No. 34422) A longitudinal section of a fibula showing involvement by the tumor Cysts may be seen at the periphery of the tumor filled with a dark, pigmented, jelly like material The bulk of the tumor is subperiosteal in location.

Areas of fibro-ostosis, either subperiosteal or endosteal in origin were seen where the tumor was invading bone. Here osteoid spicules were found, surrounded by osteoblasts and fibrous tissue (Fig. 299) the new bone thus formed being typ*ical of the process* described by us as occurring in bone cysts and giant-cell tumors. This reaction, we believe, is an attempt by the bone to heal, in a manner often noted in fractures, by a transition of fibroblasts to osteoblasts and to osteoid tissue.

In some sections, islands of tumor cells with a blood vessel at the center were surrounded by areas of necrosis, the blood supply apparently being inadequate for more than the tumor cells immediately surrounding the vessel. Such necrotic areas were referred to by Kolodny as hydropic *degeneration of tumor cells*, and by other authors as a perithaliomatous structure.

The periphery of the tumor in many cases was infiltrated by cells of the polymorphonuclear or monocytic types. This infiltration by wandering cells was most common in the cases of longer duration or *where the tumor had previously been ex*plored, and not infrequently led to an erroneous diagnosis of osteomyelitis at biopsy Eosinophiles were frequently observed along with the round-cell infiltration. An infiltration by plasmalike cells was noted in only nineteen cases of the series. This, possibly had no special relation to the tumor as sections of normal bone sometimes show such cells. On finding these cells, certain authors have suggested a relation between, this tumor and multiple myeloma.

DISSEMINATION AND METASTASES

True to the nature of malignant disease, dissemination has occurred in every case of the series which to the time of writing has terminated in death. The extent of metastases has been most difficult to determine because of the insufficient data included in many of the case reports, necropsy having been performed on twelve cases in the series. Only those cases in

which definite proof of metastases was obtained either by roentgen examination, biopsy or necropsy are included here, though death in every case was said to have been from the tumor

The most frequent sites of metastases were the lungs, the skull and the lymph latent period of from two and a half months to four years between the initial appearance of the tumor in a single bone and the involvement of other bones.

The bones most frequently involved by metastases were the skull the spine, the ribs and the scapula or the clavicle al

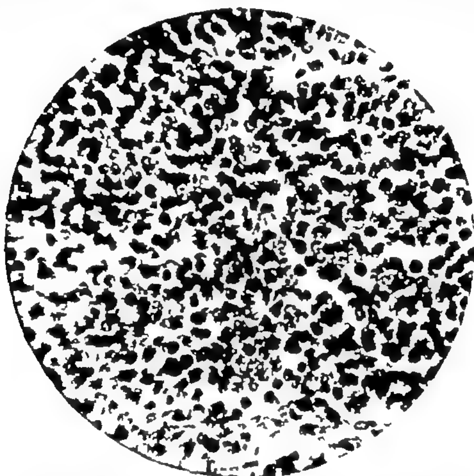


FIG. 294 (No 27039) A photomicrograph showing the characteristic cell of Ewing's sarcoma. One may note the indistinct cytoplasm and the round and oval nuclei

nodes (see Table 47 and Fig 292) The most striking feature was the dissemination of the secondary growths to other bones. Although some observers view this dissemination to other bones as proof that the tumor is primarily a multiple disease of the skeleton a form of lymphatic leukemia, with bone involvement, or neuroblastoma of the sympathetic system, with osseous metastases, in our series it was nearly always possible to obtain a definite though secondary foci in the long pipe bones also occurred. This is well illustrated by the case of a white boy aged 14, examined in this clinic and later operated upon in a neighboring city This patient had extensive metastases to the skull, the femora, the humeri and the scapulae. The lungs were involved, and he also became blind, the left eye protruding markedly from its socket. When he was first observed only the tibia was affected.



FIG. 295. (No. 24667) A photomicrograph showing the uniformity in the size of the cells. In the less compact region, the definite but irregular outline of the cytoplasm may be noted, a septum is seen traversing the tumor substance.

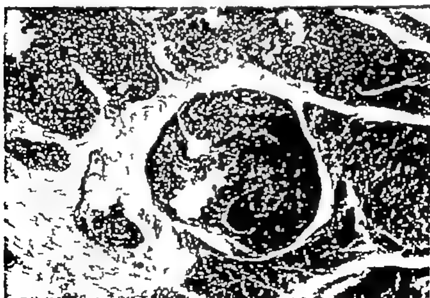


FIG. 296. (No. 24667) The formation of septa in Ewing's sarcoma, giving it an alveolar arrangement.

Involvement of the skull by secondary deposits presented unusual features. Usually the metastases form multiple nodules beneath the periosteum which indent but do not erode the outer and inner tables of the skull. In only one instance was there strated in the lungs in 40 instances. In many others, pulmonary involvement was indicated by hemoptyses, pain in the chest or a high terminal fever. In four cases, metastases to internal organs were noted without specifying the organs involved.



FIG. 297 (No. 35654) A photomicrograph showing blood vessels surrounded by tumor and the infiltration of tumor by hemorrhage. One may note the marked difference between the tumor cells and the cellular elements comprising the blood vessels.

penetration of both tables by tumor. Usually the nodules are over the vault of the cranium but the middle fossa was the site of metastasis in several instances. Multiple nodules were also found on the under surface of the dura, depressing but not invading the brain substance. Brain metastases were relatively rare.

Enlargement of the lymph nodes was reported in 18 cases, and in 10 neoplastic involvement was proved by microscopic examination. Metastases were demon-

The involvement of a single bone early in the disease with later dissemination to other bones occurs most frequently in young individuals and constitutes a striking and important feature setting Ewing's tumor apart from other tumors of the bone. In contrast to multiple myeloma or chloroma, it is unusual for the patient to present himself for examination with more than one bone involved, and if this occurs, a *single focus usually predominates in size* as well as in duration.

CLINICAL COURSE

In order to correlate the early clinical observations with the subsequent course of the disease, a brief survey of the more characteristic features of Ewing's sarcoma emphasizing the typical course of the disease, will be made.

At the onset of Ewing's tumor there is tenderness or soreness of the affected part followed by pain of either a dull aching or a sharp shooting character The patient's attention is first called to the malady by trauma, spontaneous pain or pain with formation of tumor

From this initial phase, the patients pass to a period of more continuous pain, and often the nocturnal pain may be the most severe The intervals of freedom from such attacks become less and less. In many instances, the tumors have a tendency to regress, leading the patients to think that a cure has been effected, only to recur again, becoming larger and more painful.

The tumor is often accompanied by some constitutional reaction, such as an elevation of temperature generally to 100° F., localized redness and swelling of the subcutaneous tissue or dilatation of the peripheral veins.



FIG. 298 (No. 37412) Invasion of haversian canals by tumor The tumor is extending along the vessel in one haversian canal, while other canals are completely filled with tumor cells.

On examination, a tumor is usually palpated, which varies from a small localized swelling to a large fusiform mass, and is apparently continuous with the bone. The soft parts over the tumor in most cases, are freely movable, although they may be somewhat edematous and inflamed. *The majority of the cases present an indurated mass, not of bony density but*



FIG. 299 (No. 15745) A photomicrograph showing osteitis fibrosa surrounding the invading tumor The osteoid spicules are surrounded by osteoblasts and fibrous tissue This osteoid reaction (fibro-ostosis) represents the reparative nature of all bone, no matter what the source of the injury



FIG. 300 (No. 42226) Roentgenogram of Ewing's sarcoma in the os calcis of a girl of 14 years. The tumor invasion has resulted in marked sclerosis.

with occasional slight crepitus due to the osteophytes in the tumor of the soft parts.

The roentgen examination reveals a diffuse lesion in the shaft of a long bone which is widened by periosteal and endosteal formation of new bone, the newly formed bone often showing areas of splitting and erosion. The subperiosteal tumor may be large. The marrow cavity is either narrowed or mottled by newly formed bone, and occasionally one sees subperiosteal bone spicules at right angles to the cortex, although the usual picture is a laminated formation extending along the shaft in parallel, "onion peel" fashion (Fig 302). In no case is the epiphysis primarily involved, although in late lesions it may be secondarily invaded.

The red-cell count ranges from normal to a moderate secondary anemia with or without leukocytosis. The average leukocyte count is 15,000. The differential count, in the majority of instances, is within normal limits.

In many cases, the patient gives a history of normal activity for a year or more before being confined to bed. Pathologic fracture is rare.

In two-thirds of the cases, the course of the disease is downward, although temporary relief follows irradiation or operative procedures. The usual termination is with metastases.

Loss of weight and secondary growths in other bones, often in the skull and the spine, are frequently seen late in the disease, with an occasional paraplegia. Hemoptyses, thoracic pain and fever are terminal manifestations.

TABLE 47 PRIMARY LESIONS WITH METASTASES

Patient (Surg. Path. Lab. No.)	Original Location of Tumor	Duration of Symptoms at Time of First Observation, Months	Location of Metastases	Duration of Life Following Treatment, Months
54352	Toe	6	Lungs and vertebrae	8
51612	Tibia	3	Pelvis and bladder	36
49364	Tibia	3	Skull	3
48780			Skull and lungs	
48424	Femur	6	Lungs	[illegible]
46520	Humerus	3	Lungs	8
44724	Tibia	3	Lungs	14
44068	Ilium		Lungs and skull	
44016	Rib	12	Skull	26
43769	Femur	10	Vertebra	[illegible]
43008	Humerus	6	Lungs	[illegible]
40530	Tibia, lower shaft	4	Skull, femur, lungs, humeri, scapulae	(Living after 9 mo)
34429	Tibia, upper shaft	4	Internal organs	[illegible]
34344	Femur, lower shaft	8	Humerus	20
33683	Radius, lower shaft	5	Lungs	17
31178	Fibula, midshaft		Lungs	16
30944	Tibia, lower shaft	7	Scapula, clavicle	5
30745	Fibula, upper shaft	2	Lungs	10
30064	Tibia, midshaft		Skull	21
29515	Femur, lower shaft	4½	Lungs	4½
28774	Ilium	5	Skull	(Died at operation)
28600	Humerus, upper shaft	1½	Lungs	15
28364	Fibula, upper shaft	2	Lungs, ribs, skull	6½
27511	Femur, lower shaft	8	Lungs, skull, spine	5
26916	Femur	11	Ribs 2, vertebra 1; thrombosis iliac vein	12
25897	Os calcis	24	Lungs	6
25008	Scapula	24	Glands, spine	14
23430	Fibula, midshaft	[illegible]	Glands	12
24067	Femur, upper shaft	[illegible]	Spine	18
18231	Pelvis		Glands	
13430	Humerus, midshaft	5	Glands	[illegible]
10337	Tibia, upper shaft	6	Skull	9
8172	Tibia, upper shaft		Skull, glands	2
4392	Humerus, upper shaft	3	Glands, internal organs	8
3009	Femur, upper shaft	36	Internal organs	
1807	Tibia, upper shaft	9	Vertebrae	9
64	Humerus, upper shaft	6	Glands, internal organs	5

* These patients were proved to have metastases by roentgen examination, biopsy or necropsy

DIFFERENTIAL DIAGNOSIS

A careful survey of the clinical history with available laboratory determinations

is often necessary to differentiate Ewing s sarcoma from other lesions of bone.

Among the many diagnoses first made and later revised in cases of Ewing s tumor it is interesting to note that inflammatory disease of the bone predominates. A primary diagnosis of pyogenic periostitis or osteomyelitis was made in 30 cases, tuberculosis of the bone in nine cases,† syphilitic periostitis or osteomyelitis in six cases,‡ and typhoid osteomyelitis in one case, thus showing the frequency with which Ewing s tumor is confused with chronic inflammation of the bone.

Often the intermittent pain, following trauma, or occurring spontaneously with fever suggests osteomyelitis. The roentgenogram may resemble inflammatory disease (Fig 301) The biopsy may be doubtful, the surgeon not having gone deep enough to reach intact tumor Or grossly blood mixed with tumor tissue may escape simulating pus, the condition being treated as osteomyelitis without the precaution of making sections and taking cultures.

Ewing s sarcoma is more often confused with chronic osteomyelitis than with the acute form. As was pointed out by Starr § *the acute form of osteomyelitis, in the majority of instances,* occurs between the ages of 2 and 10 and because of its sudden onset with malaise, nausea, high fever rigors, localized boring pain and a leukocyte count of from 25 000 to 30 000, should not often be confused with Ewing s tumor especially when a primary focus of infection in the skin can be demonstrated.

The chronic forms of osteomyelitis commonly show suppuration, except sclerosing osteomyelitis (Garre s type) which shows suppuration in about 10 per cent of the cases,* whereas Ewing s sarcoma shows this only after a previous operation The finding of pus or a history of furunculosis rules out sarcoma. A recent case is an exception A small infected skin lesion was present over the tibia which was affected by Ewing s sarcoma. In the roentgenograms of cases of osteomyelitis an involucrum is commonly seen, but practically never appears in Ewing s tumor



Fig. 301 (No 30184) A case of Ewing s sarcoma in the femur which is not unlike the early stage of inflammatory disease of bone

Tuberculosis of the bone,† in contradistinction to Ewing s sarcoma, is most frequent about the spine and the upper part of

Bloodgood, J C.: A brief summary of benign and malignant lesions of bone, Southern M J 19 541, 1926.

† Knaggs R. L.: The Inflammatory and Toxic Diseases of Bone Baltimore Wood, 1926, p. 57

‡ Bloodgood, J C. Differential diagnosis of periosteal lesions, Radiology 2 432, 1924.

§ Starr Osteomyelitis, in Lewis: Practice of Surgery vol. 2, Hagerstown, Md., Prior 1927 p. 4.

Bloodgood, J C.: J Radiol. 1 147 1920.

† Coley W B: The differential diagnosis of sarcoma of the long bones, J Bone & Joint Surg 10 420, 1928.

the femur though it often occurs in other locations. The age does not help in diagnosis, but the underdeveloped and undernourished condition of the patient and the slow progress and lack of severity of the symptoms together with the longer period rarely seen in Ewing's tumor which practically never shows the sequestra and draining sinuses observed in tuberculosis.

Syphilitic disease of the bone, with which Ewing's sarcoma is often confused, is more likely to occur in later life. The constitu-



Fig 302. (No. 28600) Ewing's sarcoma in a boy of 11 showing both laminated and radiating spicules of new bone.

of activity are salient features. The pain in tuberculosis of the bone may be completely relieved by immobilization, in contrast with the increasingly severe pains without relief in Ewing's sarcoma. The roentgenogram of a tuberculous bone usually shows marked destruction in the epiphyseal end, with involvement of the joint and some calcification of the soft parts (Fig 305). These are

tional reaction may not be unlike that of the small round-cell sarcoma. Syphilitic periostitis affects particularly the superficial bones (tibia, clavicle, sternum, and ulna) and usually there is multiple involve-

Chenelot, E. Sur les gommes syphilitiques simulant des sarcomes, Thèse de Lyon, 1910.
Stokes, J H. Modern Clinical Syphilology Philadelphia, Saunders, 1927 p. 685.

ment. The periosteum may be thickened, and a formation of small bony spicules, arranged perpendicularly to the cortex of the bone, may occur Kolodny and Eising pointed out that this perpendicular arrangement of osteophytes is sometimes found in



FIG. 303. (No 51670) Roentgenograms of Ewing s sarcoma of the humerus. (A) before irradiation (August, 1933) (B) after irradiation (April, 1934)

low-grade chronic infections of bone pyogenic or tuberculous. This observation is noteworthy for radiating spicules perpendicular to the cortex in a bony lesion are commonly associated with a malignant process. Ewing s tumor is no exception. The cortex in syphilitic disease of the bone may be eroded, and medullary destruction may occur (as in nonspecific osteitis) but osteophytes and increased density are more constant The serologic reaction is therefore all important in the differential diagnosis and, as was pointed out by Bloodgood and others, when a positive Wassermann reaction is present, a therapeutic test should be carried out before the tumor is explored

Clinically multiple myeloma caused confusion in four cases of Ewing s sarcoma. Multiple myeloma occurs for the most part in persons between the ages of 40 and 70 This is in contradistinction to the age incidence in Ewing s sarcoma, which ranges between 6 and 20 Multiplicity of the tumor is an outstanding feature in over 90 per cent of the cases of myeloma, including involvement of the thoracic cage, skeletal deformity and pathologic fracture. Bence-Jones

bodies are excreted in 65 per cent of the cases. In Ewing s tumor multiple involvement is rarely seen when the patient first comes under observation fractures occur

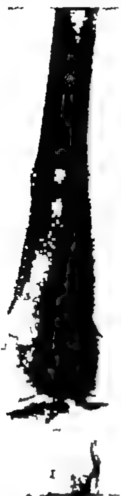


FIG 304. (No 38784) Chronic sclerosing osteomyelitis. There is a periosteal reaction above the metaphysis. As nothing in the history was diagnostic, an exploration was necessary to rule out sarcoma.

in only 5 per cent of the cases, and Bence-Jones bodies are not found in the urine. The roentgenogram rarely shows the multiple, punched-out areas seen in multiple myeloma.

Osteogenic sarcoma* in the average case is located at the end of a long bone, whereas Ewing s sarcoma appears in the shaft and does not involve the epiphysis. The formation of new bone in osteogenic sarcoma shows right-angled spicules early in the disease and practically never gives the extensive, laminated new bone paralleling the shaft seen in Ewing s sarcoma. Irradiation of the tumor offers a good therapeutic test. The Ewing tumor responds promptly to irradiation (in from one to three weeks) whereas osteogenic sarcoma is little affected. Metastatic carcinoma and so-called hypernephroma*† are infrequently confused with Ewing s sarcoma, since carcinoma occurs later in life.

Ewing s sarcoma is extremely rare under the age of four years. In children under this age Christian s disease, lymphatic leukemia, or metastases from neuroblastoma of the adrenal may be a source of confusion.

In Christian s disease of bone there is usually a characteristic syndrome consisting of multiple defects in the cranial and flat bones, diabetes insipidus or exophthalmos and enlargement of the spleen or lymph nodes. The initial manifestations, however may be confined to a long bone, more often with a well-demarcated central area of erosion, but rarely simulating Ewing s sarcoma (Fig 403) Biopsy however should reveal the characteristic mixture of lymphocytes, eosinophils and macrophages often with lipoid-laden cytoplasm. The disease resembles Ewing s tumor in being radiosensitive.

Aleukemic lymphatic leukemia in infants may produce longitudinal streaks of destruction in the shaft of the long bones, with an overlying periosteal reaction of the "onion-peel" type. Usually several bones are similarly affected (Fig 388) Microscopically the lesions may be indistinguishable from Ewing s sarcoma and respond to irradiation. The blood count shows from

* Nichols, B H.: Roentgen diagnosis of the more important tumors of the long bones, Surg Gynec. & Obst. 35 301, 1922.

* Joll, C. A.: Metastatic tumors of bone, Brit. J Surg. 11 38, 1923.

† Simpson, W M.: Diffuse vertebral metastasis of prostatic carcinoma without bony changes, Am. J Roentgenol. 15 534, 1926.

60 to 90 per cent of lymphocytes although the total white-blood-cell count may be within normal limits. This and the age of the patient establish the diagnosis.

Neuroblastoma of the adrenals with bone metastases produces multiple areas of destruction, usually wedged shaped and



Fig. 305 (No 27924) A tuberculous humerus showing marked destruction in the epiphyseal end of the bone, with involvement of the joint.

immediately under the periosteum on the shaft side of the epiphyseal line. The skull is often affected in the region of the orbit resulting in exophthalmos. Unless rosette formations are found on microscopic examination, the tumor tissue closely resembles small round cell sarcoma of bone. The lesions, however are usually smaller more widespread and somewhat less radio sensitive than Ewing's sarcoma.

TREATMENT AND PROGNOSIS

In cases in which metastases have not occurred, amputation for lesions of the lower extremity in the lower two-thirds of the femur or in the tibia, and resection for lesions in the fibula and bones of the upper extremity offer more hope of cure than does irradiation alone Irradiation is followed by radical surgery where possible

If the lesion occurs in the upper part of the femur or has become so extensive in the upper extremity that the operation of choice is not warranted, irradiation should be resorted to and continued in therapeutic doses until amputation becomes necessary to relieve pain.

When the lesion is considered operable and the clinical picture, roentgenogram and other laboratory observations are such that sarcoma cannot be diagnosed, irradiation as a therapeutic test is advised, since shrinkage of the tumor after two or three treatments is characteristic of Ewing's sarcoma.

At present, there are complete follow-up reports on 127 cases of Ewing's sarcoma. In 104 the patients are dead and in 23 cases the patients are living and appar

ently well at the time of this writing Thirteen are living over 5 years following treatment. One is alive over 4 years, one over 3 years and four died 5½, 5 and 4½ years after operation.

The methods of treatment may be divided into three main groups for analysis (1) amputation or resection with irradiation (2) amputation or resection without irradiation and (3) irradiation alone or with exploratory operation. (See Table 51.)

In 12 cases in which no adequate treatment was attempted the disease terminated fatally within an average time of 9½ months. Twelve cases involving the jaw proved fatal usually within a period of a year four dying from postoperative infection.

These results indicate that radical surgery with 19 per cent of five year cures offers more than irradiation alone in the treatment of the disease. Resection or amputation combined with irradiation offers 14 per cent of five year cures whereas irradiation alone offers 7 per cent. Since inadequate surgical treatment in fatal cases yields an average postoperative duration of life of 9½ months and irradiated cases have an average duration after treatment of 15 months, it is apparent that irradiation prolongs the life of the patient as well as alleviating the symptoms.

TABLE 48 TREATMENT BY RESECTION OR AMPUTATION WITH IRRADIATION

Surg Path Lab No	Color	Sex	Age	Location of Tumor	Duration of Symptoms at Time of Operation, Months	Duration of Life Following Operation, Months
62076	W	F	7	Humerus, lower	18	Dead 18
61674	W	M	9	Femur lower	3	Dead 48
57723	W	M	21	Femur upper	12	Dead 6
55668	W	F	7	Fibula, lower	6	Well 13 years
51566	W	F	15	Femur	1½	12
49364	W	F	8	Tibia		3
48686	W	M	25	Tibia		7
46922	W	F	8	Humerus		(Well 48 months)
46620	W	M	20	Humerus	2	8 months
37472	W	M	28	*Humerus*	36	60
35882	W	F	6	Tibia	6	26
32623	W	M	11	Radius	5	17
32770	W	M	7½	Tibia	18	16
31775	W	M	22	Fibula		16
28600	W	M	11	Humerus	1	15
27631	W	F	14	Scapula, clavicle		(Well after 84 months)
27039	W	M	9	Scapula	6	9
26916	W	M	23	Femur	11	12
26901	W	M	13	Clavicle		(Well after 84 months)
25906	W	F	19	Scapula	24	14
25430	W	F	10	Fibula	12	18
24667	W	M	11	Femur	14	18

In selecting features in the clinical history which would be of value in making a prognosis, an analysis was made of the living cases. Their ages ranged from 12 to 30 years. The site of involvement was either *the lower or the upper extremity including* the shoulder girdle. The roentgenogram showed either destruction of bone or formation of bone and sometimes both. It also disclosed diffuse involvement of the bone, and either a parallel or a right-angle periosteal reaction The gross clinical changes were not striking, and both normal white-cell counts and leukocytosis with fever were observed. Radical operation with or without irradiation and irradia

tion alone were among the methods of treatment.

All of the patients reported in this series as living today had a preoperative duration of symptoms averaging 20 months, as against [illegible] months for those who died within a year following operation. The shorter duration of symptoms apparently, therefore, indicates a more rapidly growing tumor and is ground for a grave prognosis. This reflects seriously on the hope of cure through early diagnosis and early treatment in a definite group of these cases. Apparently symptoms do not always precede the fatal stages of the disease by a sufficient margin for the purposes of therapeutics.

TABLE 49 TREATMENT BY RESECTION OR AMPUTATION WITHOUT IRRADIATION

Surg. Path. Lab. No.	Color	Sex	Age	Location of Tumor	Duration of Symptoms at Time of Operation, Months	Duration of Life Following Operation, Months
62504	W	F	2	Radius	8	1
62278	W	M	14	Humerus	0	(Well 6 years)
62210	C	F	18	Tibia	4	(Well 6 years)
62048	W	F	21	Calcaneous	2½	12
60001	W	M	22	Great toe	3	12
57708	W	M	14	Humerus	12	(Well 12 years)
57176	W	M	21	Radius		(Well [illegible] years)
54510	W	F	11	Femur	12	(Well 15 years)
54352	W	M	13	Toe	6	8
53378	W	M	35	Tibia		(Well 12 months)
51612	W	M	16	Tibia	3	(Well 36 months)
48424	W	F	10	Femur		12
43808	W	F	24	Humerus	8	12
35634	W	M	24	Tibia	12	11
34422	W	M	10	Tibia	4	53
34005	W	M	19	Humerus	84	(Well 30 months) Lost
32174	W	M	16	Femur	6	7
29286	W	F	12	Tibia	12	(Well after 78 months)
28535	W	M	24	Femur	4½	4½
28397	W	F	12	Humerus	9	(Well after 72 months)
28395	W	M	25	Fibula	9	1
28364	W	M	[illegible]	Fibula	3	6½
27511	W	M	14	Femur	6	5
26915	W	M	16	Metatarsal		35
26885	W	F	44	Tibia	4	24
26597	W	M	39	Tarsal	24	[illegible]
24927	W	M	6	Tibia	16	13
22795	W	M	22	Femur	[illegible]	(Well after 108 months)
15921	W	F		Pelvis		(Died at operation)
15838	W	M	21	Humerus	5	13
15745	W	F	14	Femur	18	5
7963	W	M	18	Fibula	12	4½
7657	W	M	16	Fibula	6	11
5172	W	F	11	Tibia		2
4393	W	F	17	Humerus	3	9
1207	W	F	[illegible]	Tibia	9	9
64	W	M	21	Humerus	6	5

Exploration does not necessarily affect the prognosis in cases in which radical operation or roentgen treatment follows exploration. In two cases in which the patients are living over five years, exploration

TABLE 50 TREATMENT BY IRRADIATION ALONE OR BY IRRADIATION WITH EXPLORATORY OPERATION

Surg. Path. Lab. N	Color	Sex	Age	Location of Tumor	Duration of Symptoms at Time of Treatment, Months	Duration of Life After Treatment, Months
62478	W	M	14	Femur	3	36
62174	W	M	12	Humerus	1	12
62124	W	F	12	Femur	2	12
61914	W	M	13	Pelvis	6	12
60966	W	M	15	Pubis	2	Well 9 years
60262	W	M	5	Femur	5	24
60202	W	F	16	Pubis	5	18
60148	W	M	24	Fibula	24	12
59786	W	F	14	Scapula		2
57718	W	M	4½	Femur	1	Well 14 years
57446	W	F		Tibia		12
57210	W	M	17	Fibula	3	[illegible]
57168	W	M	9	Ilium	3	Well 24 mos.
55732	W	M	12	Humerus	12	60
55606	—	—	—	Rib		13
54144	W	M	17	Tibia	22	(Well 12 months)
53764	W	M	44	Clavicle		18
52894	W	M	10	Femur		(Well 19 months)
52910	W	M	14	Femur		*Dead*
52234	W	M	11	Tibia		[illegible]
51870	W	M	11	Rib	3½	3
51346	W	M	32		24	24
50020	W	M	16	Femur	1	6
49746	W	F	25	Pelvis	8	9
48844	W	M	30	Rib	6	24
48780	W	M	10			8
47926	W	F	15	Femur	10	6
47032	W	M	17	Femur	5	15
46890	W	M	15	Femur	2	4
46796	W	M	3	Tibia	1	2
45826	W	M	21	Femur	12	12
44724	W	M	20	Tibia	3	14
44264	W	M	5	Foot	18	18
44068	W	M	16	Ilium	3	7
43806	W	M	18	Ischium	7	[illegible]
43788	W	M	17	Femur	10	36
43366	W	F	7	Femur	9	
35014	W	F	22	Tibia	48	(Well after 120 months)
34344	W	F	17	Femur	5	20
32910	W	M	17	Tibia	12	84
31968	W	M	17	Femur	2	39
30944	W	M	20	Tibia	7	5
30755	W	M	12	Fibula	2	10
10337	W	M	17	Tibia	6	9
5927	W	M	7	Femur	2½	2

Table 51 Results of Treatment in Ewing's Sarcoma

Treatment	No. Cases	Dead	Average Duration Fatal Cases	Well Under 5 Years	Well Over 5 Years
Radical Surgery	37	25	11 mos.	5	7
Radical surgery plus irradiation	22	18	17 mos. (1 lived 5 yrs.)	1	3
Irradiation only	41	37	15 (2 lived nearly 5 yrs)	4	3
Inadequate surgery	12	12	9½		
Primary in jaws excision or resection	12	12*			
Total	127	101		10	13

* Two cases had in addition irradiation, four died of postoperative infection.

Table 52. Summary of the Observations in Cases of Ewing's Sarcoma

Observations Simulating Tumors in General	Observations Characteristic of Ewing's Sarcoma	Observations Simulating Malignancy in General
Pain and swelling	95 per cent of cases in persons under 25 years of age	Fatal in 87 per cent of cases
	Duration of symptoms to time of treatment, 11¼ months	
Limp	Trauma in from 30 to 40 per cent five months previously	
	Occurrence only in bone	Moderate anemia
Fever leukocytosis	Femur and tibia most frequently involved	
	In long bones, shaft only primarily affected	Fever
Dilatation of superficial veins	Epiphyses involved only secondarily	
	Elliptical area of the shaft involvement	Metastases to the lungs
	Cartilaginous bone primarily involved	
Tender firm mass	Bulk of the tumor subperiosteal	Terminal cachexia
	Subperiosteum usually intact	
Occasional regression	Reactive bone both endosteal and subperiosteal	Very cellular tissue
	Cortex expanded and thickened	
	Infiltration of bone but not destruction or formation of bone primarily	
	Rapid diffusion	
	Destruction of bone late	
	Pathologic fracture rare	
	Metastases to membranous and cartilaginous bone	
	Predilection of metastases for skull	
	Tumor cells uniform in size, oval or round	
	No tumor giant cells	
	No Bence-Jones bodies in the urine	
	Regional glands involved	
	Conclusion: A neoplasm originating during the growth period in the diaphyses of bones, rapidly infiltrating bone with early diffusion, invoking both periosteal and endosteal reaction, but producing no tumor bone or direct erosion of bone	

was done before the operation of choice was performed. In one case of curettement followed by irradiation, the patient is living over four years after treatment,* and in another case the patient is well 10 years later. In one case in which the femur was explored the patient is living 6 years after several courses of irradiation. In 12 cases in which an exploratory operation was performed without further treatment, death occurred in from 1 to 22 months.

* This patient died 4½ years after treatment of metastases, but without signs of local recurrence.

NATURE OF EWING'S TUMOR

In order to arrive at some conception of the nature of Ewing's tumor we have attempted a summary in Table 52.

The facts listed in Table 52 point to the conclusion that Ewing's tumor is a primary sarcoma of bone. In favor of this is the age incidence of the tumor, its location in bone, the cellular nature of the pathologic changes, the metastases and the high percentage of fatality. Against the opinion, occasionally voiced, that this lesion is a

metastatic tumor arising primarily out side of bone is the failure to demonstrate such a primary focus in any of the cases studied and the occasional cures by ampu tation. The cellular morphology of this tumor also does not resemble that of spherical contour of medullary tumors. Multiple myeloma, metastatic carcinoma and chloroma with leukemia all show a central location with a more or less spherical growth widening the medullary cavity These tumors occupying the marrow cavity



FIG 306. (No. 50020) Roentgenogram of Ewing s sarcoma occur ring in the upper femur The cells of this tumor were grown in tissue culture (see Fig 312)

carcinoma, nor does the age of the patient suggest such a disease. The age distribu tion is against metastatic neuroblastoma.

The summary of the observations in Table 52 is against the belief that the tumor is a myeloma originating in the marrow In the first place, as pointed out elsewhere, the elliptical area of shaft involvement with the bulk of the tumor lying subperiosteally does not resemble the usual central and show early destruction of bone and in the majority of them Bence-Jones bodies have been demonstrated. The Ewing tumor in contrast with these neoplasms, most frequently shows a narrowing or occlusion of the medullary cavity with both endosteal and subperiosteal formation of new bone early in the disease, which would seem to indicate that the tumor has not a primary medullary origin The absence of marked

changes in the blood and of Bence-Jones bodies in the urine is against this assumption. Gross specimens and microscopic sections cut transversely through the bone usually show only a small portion of the tumor tissue in the marrow cavity The rapid extension of the Ewing tumor in a plane parallel to the axis of the shaft indicates that the tumor does not expand freely and points to the growth being either intra cortical or subperiosteal in origin

The majority of the observations summarized in Table 52 could be explained by either an intracortical or a subperiosteal origin of the tumor If the neoplasm is primary in the haversian systems, this would explain the rapid infiltration by the tumor producing both early endosteal and subperiosteal reactions of new bone. It would explain, also, the distribution of the tumor under the periosteum and into the medullary cavity in the later stages, and account for the widening of the haversian canals and the splitting of the layers of the cortical bone so frequently observed under the microscope (Fig 314) However conclusive microscopic proof of the origin of the Ewing tumor in the haversian canals is lacking. While specimens usually show the tumor pervading these structures, we have been unable to determine whether the tumor arises here or secondarily infiltrates into these channels.

The assumption that the Ewing tumor arises in a subperiosteal locality may be maintained, with probably equal validity from the facts observed. The active subperiosteal layer which ceases at the epiphysis and atrophies in adulthood would account for the involvement of the shaft only in youthful patients. This location would account also for the fact that the bulk of the tumor is under the periosteum, for the tendency of the haversian systems to be infiltrated, and for the reactive formation of new bone of both endosteal and subperiosteal origin. It would explain also the tendency of the tumor to extend up and down the shaft rather than to form a spherical growth. It would also fit in w the absence of Bence-Jones bodies in urine and the lack of marked change the blood.

On the basis of these observation is clear that the tumor whether prima



Fig. 307 (No 38672) Roentgen gram of a reticulum-cell variant Ewing s sarcoma occurring in the low end of the femur

intracortical or subperiosteal is not m lary nor primarily osteolytic, as is rently believed. The rarity of patho fracture, the location of the tumor roentgen and the gross observations a against this assumption, and destru of bone is always a late manifestatic the disease.

The explanation that the tumor about the perivascular lymphatics in haversian canals is not altogether unfea and would give this tumor an intraco origin Tumor cells are frequently obs

in this region (Fig 315) but sections of normal bone do not show cells of the Ewing type from which the neoplasm might arise and the anatomy of the lymphatics in this region is not established.

There are grounds for suggesting that Ewing's tumor is a primary lymphoma of bone. From the roentgenologist s point of view Ewing s sarcoma responds like tumors of the lymphoid group in that it reacts readily to irradiation. Histologically also the cells resemble lymphoblasts and lym phocytes. In the roentgenogram the early picture is not unlike the multiple bone in volvement seen in lymphatic leukemia where there is a laminated periosteal re-action overlying the shaft. In tissue cul ture the characteristics are lymphoid rather than endothelial. In addition to the lym-phoblasts seen in tissue culture there are cells with small prolongations of cytoplasm which are like the reticulum cell which histologists believe to be the forerunner of the lymphoblasts in lymph nodes. More-over certain atypical sarcomas, primary in bone and resembling clinically Ewing s tumor are microscopically identical with lymphosarcoma of the reticulum-cell type occurring in lymph nodes. The tendency to involve other bones rather than to metastasize to other organs is suggestive of lymphosarcoma of lymph nodes, which usually spreads to other lymph nodes and reticulo-endothelial organs before affecting the viscera.

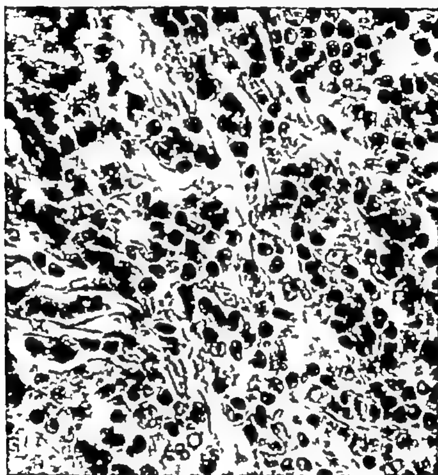


FIG. 308 (No. 38672) Photomicrograph of the case shown in Figure 307

Some of the cases classed as Ewing's sarcoma are metastatic foci of lymphatic or myeloblastic leukemias, others are met

astatic neuroblastoma. Willis has twice presented cases in which a diagnosis of Ewing s sarcoma was made on the basis of roentgen and microscopic findings in a long bone In one of these, the adrenal was involved at autopsy In another a large paravertebral tumor was found at post mortem. Willis believes these are examples of metastatic neuroblastoma to bone and that all cases of Ewing s sarcoma are erroneously interpreted as primary and that they represent secondary deposits of neuroblastoma or leukemia.

Classification of Ewing s sarcoma as primary lymphoma of bone can be supported from the standpoint of histogenesis by the atypical cases, discussed below which show a transition from reticulum cells through lymphoblasts to lymphocytes, the small lymphocyte constituting the small round cell which predominates in typical cases. This conception of the histogenesis with an origin of the tumor from reticulum cells does not place these growths in the reticuloendothelial class as suggested by Oberling. Melnick has pointed out that the cells of this sarcoma do not show the properties of reticulo-endothelial cells since the characteristic motile and actively phagocytic macrophages are lacking.

The more primitive reticulum cell which lines the sinuses of lymphoid tissue and which gives rise to the cells of the lymphocytic series rather than to endothelium or macrophages is the most likely cell of origin in Ewing s sarcoma. Unfortunately the occurrence of such tissue in the normal haversian spaces and in the subperiosteal regions of bone has not been thoroughly studied.

ATYPICAL EWING'S SARCOMA

A group of primary sarcomas of bone in young individuals running the clinical course of Ewing s tumor with pain, dysfunction, tumor fever and leukocytosis and responding temporarily to irradiation, presents atypical features in the roentgenogram and under the microscope. This rather rare group of sarcomas involves the metaphyseal end of the long bones rather than the shaft, and tends to invade the marrow cavity early producing bone destruction without marked periosteal reaction The tumors are composed of cells which vary in size many having pointed



FIG. 309 (No 46686) Roentgenogram of reticulum-cell variant of Ewing s sarcoma.

prolongations of cytoplasm. Tumor giant cells resembling the Dorothy Reed cells found in Hodgkin s disease are scattered in the tissue. Histologically the tumor is identical with reticulum-cell sarcoma of lymph nodes (Fig. 310) In other instances the tumor is composed of relatively large or medium-size lymphocytes which may be nearly twice the size of those found in typical Ewing s sarcoma (Fig 308) Formerly these cases were grouped with large, round cell sarcoma of bone and similar cases have

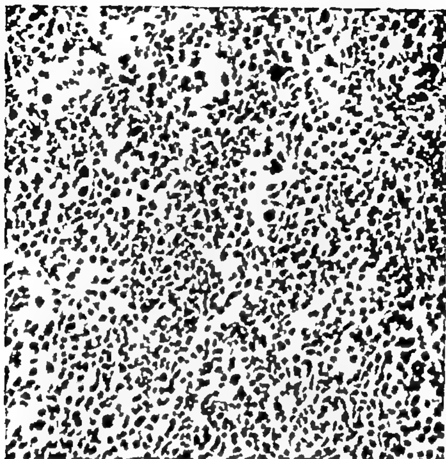


Fig. 310 (No 48686) Photomicrograph of reticulum-cell variant of Ewing's sarcoma occurring in the metaphysis of the tibia.



Fig. 311 (No. 58769) Roentgenogram of Ewing's sarcoma of the soft parts secondarily invading the bone of the foot.

been reported in the literature as undif ferentiated osteoblastic sarcoma. Their response to irradiation and the absence of osteoid substance or any sign of bone production on the part of the tumor cells favor their inclusion in the group of Ewing s sarcoma



Fig. 312. (No 50020) Tissue culture obtained from Ewing s sarcoma of the upper femur The elongated angular cells in the bottom of the photograph resemble the recticulum seen in atypical Ewing s sarcoma (Fig. 309)

Most of these cases, because of their rapid clinical course, atypical appearance in the roentgenogram and systemic reactions, were regarded as acute osteomyelitis at the time of treatment. Nearly all of them proved fatal. The following case is char acteristic of the group

The patient, a white male aged 25 was admitted to the hospital May 5 1931. In 1924 he had an injury to his right knee while playing football This was not serious and never incapacitated him. In January 1931 pain began, which gradually in creased the knee was slightly swollen and could not be straightened. Roentgen ex amination showed areas of destruction in the head of the tibia, which were inter preted as osteomyelitis (Fig 309) The pa tient s temperature was 100 degrees and his white-blood-cell count 10,500 On May 10 1931, the affected region of the tibia was ex plored. Both biopsy and culture were taken. These were both reported positive for osteomyelitis. The patient was readmitted May 28, 1931, because of increased severity of the pain. The fever was more pronounced (100 to 103 degrees) and the

white-blood-cell count 17 600 On August 4, 1931, curettement was performed fol lowed by maggot therapy Tissue removed at the second operation was referred to this laboratory for diagnosis. A report was made of atypical Ewing's sarcoma of the reticulum-cell type (Fig 310) The patient was readmitted February 19 1932. The leg was amputated. On June 6 1932, the pa tient had a mass of enlarged lymph nodes in the right groin removed. These showed metastatic involvement. There was rapid recurrence of the tumor in the surrounding muscle and soft parts. In spite of deep roentgenotherapy administered to this region in August, 1932, the patient developed pulmonary metastases. He died April 19 1933 Among the recent cases of the reticu lum-cell variant of Ewing's sarcoma, ir radiation rather than surgery has been the treatment of choice. To this has been added injections of testosterone, three times a



FIG. 313 (No. 32770) (A) shows the involvement of a tibia by Ewing's sarcoma with much periosteal reaction and a mottling of the marrow cavity This tumor was explored for biopsy the ex ploratory operation being imme diately followed by irradiation. (B) shows the effect of irradiation on the tumor Marked sclerosis has occurred in both the shaft and the periosteal region, reactive bone having formed in abundance on retardation of the growth of the tumor

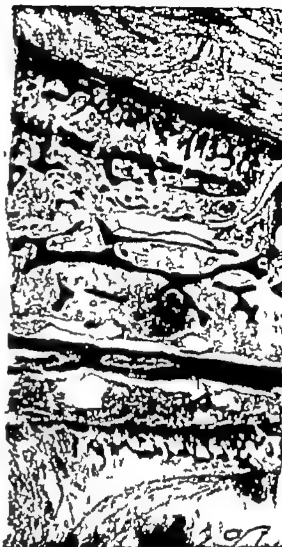


FIG. 314. (No 27039) (A) Low-power photomicrograph of a section taken through the body of the scapula in a case of Ewing's sarcoma. Note the splitting of the layers of cortical bone, the widening of the haversian canals and the spicules of bone at right angles to the cortex extending inwardly from the region of the periosteum. There is a small nest of tumor cells in the medullary cavity but the bulk of the tumor is between the cortex and the reactive bone of the periosteum near the point of medullary involvement in the lower half of the picture.

week to females, and injections of estrogens to males. These cases have proved more radiosensitive than the typical Ewing s tumor and results to date are encouraging ated stage in the evolution of Ewing s sar coma indicating an origin from reticulum cells which differentiate into lymphocytes after passing through a lymphoblastic



FIG. 315 (No. 32174) A photomicrograph showing a por tion of the cortex in Ewing s tumor The haversian canals have been widened by the infiltration of tumor which has pervaded the bone by means of the perivascular lymphatics within the haversian canals.

Two cases have survived the five-year period.

Although these cases are infrequent and constitute less than 10 per cent of those classed as Ewing s sarcoma, they furnish important evidence concerning the histogenesis of the entire group These atypical cases we believe represent an undifferenti stage. The designation, Ewing s sarcoma, reticulum-cell variant, is suggested for this group

Ewing s Sarcoma of the Soft Parts. Rapidly growing malignant tumors which are mi croscopically identical with Ewing s sar coma may form in the soft parts, appar ently arising immediately adjacent to the

periosteum. If the tumor is allowed to progress for some time before surgical intervention, secondary involvement of the bone is the rule (Fig 311) On the other hand, some of these tumors at the time of excision did not invade the neighboring bone and were attached to the periosteum only by an occasional strand of fibrous tissue. These tumors pursue a clinical course similar to Ewing's sarcoma and are also radiosensitive The following case is representative of ten tumors in this laboratory which have been classified as Ewing's sarcoma arising in the soft parts.

The patient was a white boy aged 12 years. A rapidly growing tumor appeared in his left forearm three months previously The mass was neither painful nor tender and was about the size of an adult fist. Roentgen examination of the arm showed the tumor to be in the soft parts adjacent to the bone but without bone involvement. On August 27 1934, a complete excision was performed. The mass was adherent at two points to the deep muscles and was incorporated in the palmaris longus. The capsule was cut into at one point where it appeared attached by a strand of connective tissue to the periosteum. The bone itself however was not involved. Microscopically the tumor tissue was composed of proliferation of fairly uniform cells resembling lymphosarcoma. In September 1934, the patient received a prophylactic course of roentgen therapy In May 1935 a mass about the size of a fifty cent piece was palpable near the scar of the previous operation. No enlarged lymph nodes were palpable in the regions draining the affected arm or elsewhere. Further roentgeno therapy was given and in November 1935 there is no palpable tumor in the arm and roentgenograms of the chest are negative for metastases. This patient died in 1936.

These variants have led some observers to suggest that Ewing's sarcoma is not a definite pathologic entity but instead represents a conglomeration of several entities, such as monocytic or lymphocytic leukemia in the subleukemic phase, undifferentiated synovial sarcoma and metastatic neuroblastoma to bone

SUMMARY

Ewing's tumor is a neoplasm occurring as a rule in the first two decades of life, involving most frequently the tibia and the femur and may metastasize late in the disease to other bones. The disease never primarily involves an epiphysis. It shows the usual symptoms of sarcoma of bone of pain and tumor followed by dysfunction The duration before treatment is about ten months. It may give the systemic reactions of fever and leukocytosis. In the roentgenogram the disease first widens the shaft of the bone by stimulating new bone formation in parallel layers endosteally and subperiosteally raising the periosteum in "onion peel" fashion. Later the tumor which arises intracortically or subperiosteally produces areas of bone destruction in the medullary cavity and subsequently in the cortex. Histologically the tumor is composed of small, round cells with dense nuclei and scanty cytoplasm simulating a lymphosarcoma. Histogenetically, the growth appears to arise within the lymphatic channels of the bone. Radical surgery gives the best results in treatment, yielding about 19 per cent of permanent cures. The average postoperative duration of life is 16 months in fatal cases. While a few cures may follow irradiation alone, this form of treatment should not be persisted in after six weeks if definite results are not achieved. Irradiation, however provides a good therapeutic test and the best available palliative therapy Irradiation combined with radical surgery yielded 14 per cent of five-year cures.

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18

Multiple Myeloma

As the name implies, multiple myeloma not only produces extensive involvement of the skeleton but the systemic manifestations of the disease are particularly widespread. Changes in the central nervous system, the thorax and lungs, the kidneys, and in the blood picture are frequently prominent features in cases of multiple myeloma. A careful pathologic study shows that all these various phases in the symptomatology and the physical findings are secondary to the lesions originating in the bones. Prior to the widespread use of roentgenograms in the diagnosis of bone lesions, the recognition of multiple myeloma was made usually at the autopsy table, and reports of the disease were rare, although the first observation in the literature was recorded more than a hundred years ago. While the roentgenogram is not diagnostic, the introduction of laboratory tests, which include an analysis of the urine for Bence-Jones proteins, the determination of the blood protein, and a sternal marrow puncture for the myeloma cells facilitate the diagnosis of the disease.

HISTORICAL BACKGROUND

Dr William McIntyre in reporting the first case of multiple myeloma adequately described in the literature, relates the following

> Mr M— a highly respectable tradesman, aged 45 placed himself under my care on the 30th of October 1845 On taking charge of the case I had the advantage of meeting Dr Watson, whom the patient had consulted at the beginning of the preceding summer
>
> On the 15th (Nov., 1845) Dr Bence-Jones, who had been for some time engaged in examining the composition of the patient's urine met us in consultation At his suggestion alum was added to the tonics in use with the view of checking the exhausting excretion of animal matter (The animal matter referred to is now known as Bence Jones bodies.)

The foregoing citation brings together the names of McIntyre, Watson and Bence-Jones, who were jointly responsible for the study of this case. In his report, McIntyre also refers to Dalrymple, who undertook the "microscopical examination of the two affected ribs," and communicated his observations to the Dublin Quarterly Journal of Medical Science.

The three reports of Dalrymple, Bence Jones and McIntyre, in the hands of subsequent investigators, were not accorded the same degree of attention Had this been otherwise, perhaps Dalrymple instead of Rustizky (writing twenty seven years later in 1873) might have been credited with the

histologic study of this disease, and Mc Intyre instead of Kahler (whose work appeared thirty-nine years later in 1889) cited as the first to describe multiple myeloma in connection with the excretion of Bence-Jones bodies. Between 1848 and 1873 only three probable cases were added to the literature. These reports were made by Herman Weber in 1867 by Crudeli in 1871 and by Adams and Dowse in 1872. After Kuhne, in 1882, the work of Kahler in 1889 was responsible for calling attention to this disease

In Italy the works of Bozzolo in 1897 and 1898 awakened a series of contributions (over 40 case reports) paralleling the stimulus lent to German clinicians by Kahler's article (followed by some 135 case reports) Although English works must be granted the priority in this field, their contributions have not been so numerous as the German.

Perhaps the best reviews on the subject are to be found in Martini's article from Italy in Policlinico and Wallgren's article from Sweden. A complete bibliography has been published elsewhere by the authors (Geschickter and Copeland)

ETIOLOGY

Multiple myeloma is a disease of later life approximately 80 per cent of all cases occurring between the ages of 40 and 70 with the peak of incidence at 55 In this respect, it closely follows other malignant diseases, coinciding almost exactly with the age incidence of a series of over 500 cases of metastatic carcinomatous skeletal tumors reviewed in the next chapter

Young adults are not spared, although we have been able to find only eight cases occurring in adults under 35 Williams, Evans and Glynn reported one case in a patient aged 30- Moore reported one in a patient aged 27 and Haberfeld and Lordy one in a patient aged 22, all three cases being microscopically verified. Since the previous edition of this book, we have observed two patients in their early twenties.

Some uncertainty is attached to the occurrence of multiple myeloma in children. Cases reported by Roman (1912) and by de Elizalde and Llambias (1913) are not considered myeloma by Wallgren A case reported by Gilmore (1925) and submitted to the Bone Registry (serial 280) was diagnosed myeloma by Woods and Smith with Bloodgood, Wolbach and Mallory dissenting The two cases reported by Berkheiser (1924) resemble Christian's disease in one instance, and Ewing's endothelial myeloma in the other The ages of the children in the various cases reported vary from 2 to 12½ years.

In regard to sex, the occurrence of myeloma in males, roughly estimated, is twice as frequent as in females. Anders and Boston reviewing 33 cases of myeloma, found 80 per cent in males Wallgren found 68 per cent of males in 98 cases, and in our series of cases 70 per cent occurred in males.

The occurrence of myeloma appears to be widespread Reports are numerous from England, America, Germany and Italy Cases have been described in all parts of Europe—Scandinavia, Russia, Holland, France and Switzerland—in Canada, in Australia and in South America. MacCallum and Hamburger have described the disease in a Negress, and Jacobson has found it in a Chinaman. The disease apparently does not favor any particular strata of society nor does any special climate or region appear to be immune.

Many unsatisfactory attempts have been made to estimate the incidence of myeloma. Symmers and Vance found 3 cases among 4,000 autopsies at the Bellevue Hospital, and in 9 000 autopsies at the Johns Hopkins Hospital there were 4 cases.

Multiple myeloma occurs in about 0 03 per cent of all types of malignancy This incidence is based on life insurance tables in which sarcoma in general is seventh in frequency in the list of malignancy or 3.5

* Authors referred to will be found in alphabetical order in the bibliography appended to this chapter

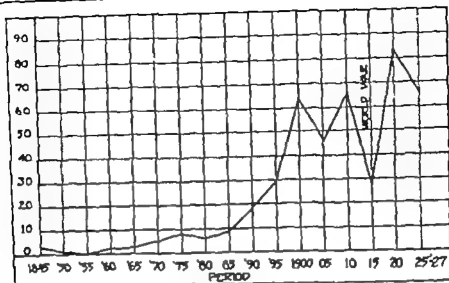


CHART 11 Distribution of 425 reported cases of myeloma by five-year periods from 1845 through 1927

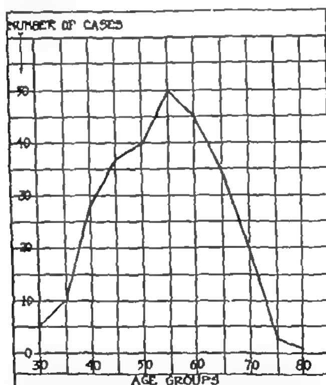


CHART 12. Age incidence in cases of multiple myeloma.

per cent, with sarcoma of the bone one third of this, or about 1 per cent. Among 400 cases of sarcoma of the bone in the surgical pathologic laboratory at the Johns Hopkins Hospital, 3 per cent were multiple myeloma. These statistics, based upon autopsy records, understate the frequency of the disease.

There is little that can be said concerning the causative agents of multiple myeloma. Meagerness in the majority of the case reports precludes reliable conclusions

drawn from the previous history of these patients.

With respect to trauma, so much stressed in tumors of the bone, there is more plentiful, if not more convincing, evidence at hand. Although trauma as a factor in the disease was probably not sought for in a considerable portion of the cases, we found it in the history of 20 per cent. When recorded in some cases, it precedes the disease by an interval sufficiently long to render its significance questionable. More frequently the justifiable conclusion is that the trauma was superimposed on a preexisting diseased state, since it was of such slight nature that in healthy persons symptoms could hardly have been produced.

Infection has been cited as a causal agent. In patients with myeloma, the combined incidence of influenza, malaria and typhoid is approximately that of trauma. When one considers the frequency of these infections among all classes of patients, their special significance for this disease is doubtful. Tuberculosis, syphilis, osteomyelitis and infectious arthritis are found associated with myeloma and sometimes coexistent with it. These diseases have no demonstrable connection with the etiology of multiple myeloma and their association with it is coincidental.



FIG. 316 (No 42108) Roentgenogram showing typical punched out areas of bone destruction in a case of multiple myeloma.

From time to time, theories regarding the infectious nature of myeloma have been proposed and the occasional febrile course of the disease is stressed. More plausibly the elevations in temperature can be ascribed to intercurrent infections. All in all, the etiologic obscurity that is attached to malignancy seems to extend in no less degree to multiple myeloma.

The modern tendency is to associate the plasma cell of multiple myeloma with the function of globulin formation in the bone marrow In this way the frequent elevation of globulin in the blood plasma in multiple myeloma is explained. Some authors, such as Snapper have suggested that a disturbance in the plasma proteins precedes the development of the disease and that in some obscure way this incites the bone-marrow cells responsible for globulin formation to tumor proliferation.

CLINICAL CHARACTERISTICS

PAIN

Pain is the outstanding symptom of myeloma which causes the patient to consult a physician. Although, when its course is viewed in its entirety the pain is seen to be typical in many of its features, the initial phases are particularly vague and indefinite

Pain at the onset of the condition is characterized as rheumatic. It is wandering and intermittent, but is generally confined to the back. In 70 per cent of the cases the pain is found in the lumbar or sacral regions in 20 per cent, in the chest over the ribs or sternum in 5 per cent, in the legs, arms or shoulders, and in 5 per cent, in other parts of the body

Often the pains are described as neuritic. Girdle sensations, or radiation down the legs are common. One of the chief features of the pain is aggravation by motion or pressure. Although subject to remissions, it may have acute exacerbations.

Sharp accentuations of pain, brought on by sudden movement or muscular exertion, call the patient's attention to the severity of his illness. Most frequently such an unexpected climax of pain is brought about by the strain of lifting a heavy load or by some inexplicable fall These attacks are exceedingly severe and leave the patient in a state of prostration and collapse. In one case, the patient was chopping wood, when an effort precipitated pain which felled him to the ground, where he lay motionless for many minutes in a state of great pain and anxiety In a case cited by Kahn the sudden halting of a train in which the patient was seated was sufficient to bring on the attack. One of Wallgren's patients was seized by pain when going down some steps he tumbled headlong down the remainder of the flight and sustained a fracture of the radius.

The result of such an attack leaves the patient for the next few hours or days with severe pains in the lumbar and sacral regions, or over the lower ribs. From this stage of relatively intense pain the affliction passes over into a period of intermittency an asymptomatic period which may last as long as several months or even a year This period in which the malady is apparently arrested is fairly characteristic of multiple myeloma, and it is during this interval that many of the patients have been discharged from the clinics, to fall into the hands of charlatans when the later stages of the disease become manifest.

During the final stages of the disease the pain reaches a climax in which it is at a maximum. It is here that portrayals of suffering of the most agonizing sort are to be found in the literature, and it is in this stage that complicating root pains, paresthesia and neuralgia appear

We may sum up the characteristic course of the pains in the following outline

Stage 1 Intermittent, insidious wandering pains, rheumatic or neuralgic, radiating or girdle in character worse on motion or pressure

Stage 2 A dramatic incident of aggravation, with increase of intensity marked by collapse prostration and bone-breaking pains.

Stage 3 Subsiding intermittent pains.

Stage 4 Relative freedom from pain with symptomatic relief

Stage 5 Recurrent, progressively intense pain, proceeding to death—complicated by neurologic manifestations.

In almost every case studied, the course of pain described here had been manifest in one or more of these stages. Occasionally the terminal stage only will come under

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Pain at the onset of the condition is characterized as rheumatic. It is wandering and intermittent, but is generally confined to the back. In 70 per cent of the cases the pain is found in the lumbar or sacral regions in 20 per cent, in the chest over the ribs or sternum in 5 per cent in the legs, arms or shoulders, and in 5 per cent, in other parts of the body

Often the pains are described as neuritic. Girdle sensations, or radiation down the legs are common. One of the chief features of the pain is aggravation by motion or pressure. Although subject to remissions, it may have acute exacerbations.

Sharp accentuations of pain, brought on by sudden movement or muscular exertion, call the patient's attention to the severity of his illness. Most frequently such an unexpected climax of pain is brought about by the strain of lifting a heavy load or by some inexplicable fall. These attacks are exceedingly severe and leave the patient in a state of prostration and collapse. In one case, the patient was chopping wood, when an effort precipitated pain which felled him to the ground, where he lay motionless for many minutes in a state of great pain and anxiety In a case cited by Kahn the sudden halting of a train in which the patient was seated was sufficient to bring on the attack. One of Wallgren's patients was seized by pain when going down some steps he tumbled headlong down the remainder of the flight and sustained a fracture of the radius

The result of such an attack leaves the patient for the next few hours or days with severe pains in the lumbar and sacral regions, or over the lower ribs. From this stage of relatively intense pain the affliction passes over into a period of intermittency an asymptomatic period which may last as long as several months or even a year This period in which the malady is apparently arrested is fairly characteristic of multiple myeloma, and it is during this interval that many of the patients have been discharged from the clinics, to fall into the hands of charlatans when the later stages of the disease become manifest.

During the final stages of the disease the pain reaches a climax in which it is at a maximum. It is here that portrayals of suffering of the most agonizing sort are to be found in the literature, and it is in this stage that complicating root pains, paresthesia and neuralgia appear

We may sum up the characteristic course of the pains in the following outline

Stage 1 Intermittent, insidious wandering pains, rheumatic or neuralgic, radiating or girdle in character worse on motion or pressure.

Stage 2 A dramatic incident of aggravation with increase of intensity marked by collapse, prostration and bone-breaking pains.

Stage 3 Subsiding, intermittent pains.

Stage 4 Relative freedom from pain with symptomatic relief

Stage 5 Recurrent, progressively intense pain, proceeding to death—complicated by neurologic manifestations.

In almost every case studied, the course of pain described here had been manifest in one or more of these stages. Occasionally the terminal stage only will come under

observation, and this will give the appearance of an acute onset. In over 75 per cent of the cases, however the course of the disease, while averaging in duration between one and two years, is insidious in its onset.

affects the red-marrow bones, and is practically never confined to an extremity through the course of the disease.

One of us has reported a case in which the upper femur alone was the seat of plas-

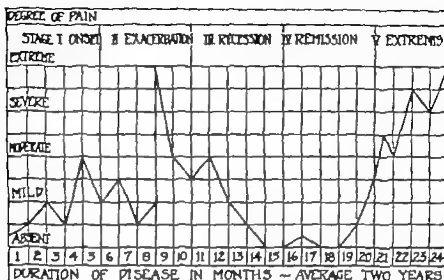


Chart 13. Course of pain in cases of multiple myeloma.

Tumor Formation

Not infrequently tumor formation is the initial symptom that calls attention to this disease.

The distribution of the tumors is one of the diagnostic features of multiple myeloma. The multiplicity of the tumors is a cardinal point. When the disease has been found in a single focus, autopsy was not performed, although thorough roentgen studies were made in some. There is multiple involvement of the ribs, sternum or clavicles and spine in 90 per cent of all cases. In other words, in nine of ten patients with myeloma there are tumors of the ribs, sternum and spine of the ribs, clavicle and spine, or of the ribs, sternum, clavicle and spine. Forty per cent of these patients have, in addition either involvement of the skull or the extremities about the shoulder or pelvic girdle besides involvement of the trunk.

Although solitary foci of multiple myeloma have been reported, exceptions are so rare that one is justified in stating that myeloma is always multiple in distribution,

mocytic myeloma this was verified at operation. Five years later the patient had involvement of the lumbar vertebrae and succumbed to the disease. In another case referred to the authors the only demonstrable mass involved the wing of the ilium (Fig. 324) While no other lesions were found at autopsy it is entirely possible that myeloma cells could have been demonstrated in the marrow had smears been taken. Paul and Pohle collected 45 cases of solitary myeloma from the literature in 1942. While a single focus of bone involvement was the outstanding feature of these cases, sternal marrow punctures in such instances revealed that the myeloma cells were more widely spread in the red marrow

The tumors vary in size from that of a pinpoint to that of an orange and more generally from a pea to a hazelnut in size. The patient may be made aware of such tumor by tenderness, pulsation, mere lump or pathologic fracture. Occasionally a diffuse atrophy or so-called myelomatosis may not give evidence of tumor formation (Aschoff

Boggs and Guthrie, and Wallgren) If the larger tumors are in the sternum, clavicle ribs or skull, their true nature is probably discovered earlier than when such masses are confined to the spine, where they are obscured by mere stiffness or beginning kyphosis.

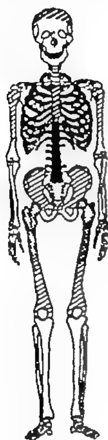


FIG. 317 Incidence of skeletal involvement according to location. The solid black areas indicate the most frequent sites; the heavy diagonal lines, the common sites the checked areas, the fairly common sites, the light diagonal lines, the occasional sites, and the white areas, rare sites.

The tumors have been variously described as elastic, yielding, pliable or malleable. Often a parchment like crepitation may be elicited over the thin bony shell of the tumor and where a mass is not made out, the bones give the sensation of yielding and fragility Occasionally true pulsation may be observed as in the case of Rustizky or semifluctuation made out as observed by Bruce.

Although painless tumors have been described, it is usual for the later stages to be extremely painful The mere touch of the hand, the pressure of a stethoscope or the weight of the bed clothing may be unbearable. The approach of the physician to the bedside is often sufficient to make the sufferer cringe with fear of impending pain.



FIG. 318. (No. 38174) Gross specimen of myeloma in the shaft of the femur

A peculiar feature of some of the tumors is their tendency to decrease spontaneously in size, with disappearance and reappearance, as cited by Thomas. Perhaps this variability in size is associated with hemorrhage and the absorption of hemorrhage, as, on section, these tumors are exceedingly vascular This quality also explains the occasional pulsating and semifluctuant characteristics.

DEFORMITY

Deformity of the bones has long been recognized (since Kahler) as an accompaniment of multiple myeloma, but its distinctive peculiarities have not been sufficiently emphasized, as is indicated by the frequency with which this disease is confused with Paget's osteitis deformans, osteomalacia and von Recklinghausen's fibrocystic disease.



FIG. 319 (No. 38220) Gross specimen of humerus showing central location of multiple myeloma.

In cases of myeloma 60 per cent show thoracic deformity and when this deformity extends to the extremities, it is confined *to the regions* of the shoulder or pelvic girdle. Bowing of the tibiae as in Paget's disease, marked bending of the extremities as in osteomalacia and the globoid sites of malunion in the lower limbs that are found in von Recklinghausen's disease practically never occur in cases of myeloma. The deformities are peculiarly thoracic, and their favorite sites are about the sternum and the spine.

At the sternum, in addition to tumor there is often a sinking in at the angle of Ludwig, or more rarely a "wavy" deformity of the gladiolus. Parasternally along the *ribs and at the clavicles, multiple small* tumor nodules may be palpated, and this multiple involvement is so frequent (approximately 50 per cent) that we have termed it the parasternal rosary to call attention to its diagnostic importance.

In the spine, flattening of the lumbar curve, dorsal kyphosis, and actual telescoping of the spinal column due to infraction and collapse of the vertebral bodies occur. In Marckwald's case there was a maximum shortening of 20 cm., while in a case cited by Kahler and one of our own there was nearly an equal amount. Scoliosis is not a rare observation.

These deformities of the trunk lead to a characteristic habitus or stance. The patient stands with protruding abdomen, his bulging lower ribs resting on the pelvic brim his shoulders braced back and his feet set at a wide base to aid in maintaining his equilibrium. Fatigue and pain come on rapidly with standing. The patient walks with the utmost deliberation and caution, if his affliction does not confine him to bed. In some cases, the chin rests continually on the chest, giving rise to decubitus ulcers.

Less commonly when the skull is involved, there may be interference with mastication. In a case of Anders and Boston the teeth fell out. In Schmorl's case, the skull is reported to have increased 8 cm. in size during the course of the illness—a rare occurrence in cases of myeloma and more typical of Paget's disease.

FRACTURE

The bone destructive nature of the tumors in myeloma is exemplified by the frequency of pathologic fracture. Although often escaping clinical recognition, in no other tumor of the bone does fracture occur in so large a proportion of cases.

In a study of malignant tumors of the bone, we have found 33 per cent of pathologic fracture in metastatic carcinoma, 62 per cent in multiple myeloma, and 8 per cent in osteogenic sarcoma.

While pathologic fracture may cause the symptom of onset, it is seldom recognized in itself as an initial sign of the disease. Wallgren's case was diagnosed clinically as exudative pleurisy At autopsy fracture of the fifth rib was discovered, with a large subperiosteal hemorrhage. In another case an early symptom was pain from fracture of the rib which was only discovered a year later by careful roentgen study

The distribution of fractures in this disease is striking. In other tumors of the bone pathologic fracture occurs almost exclusively in the weight-bearing bones of the lower extremities. In contrast to this the principal sites for fracture in multiple myeloma are in the ribs (involved in over 50 per cent of the cases) The clavicle and sternum are less frequently affected. In two of our own cases the clavicle was involved as in the cases of Symmers, Moore, Bruce, and Meyerding. Fractures occurring in the sternum are described (Williams, Evans and Glynn)

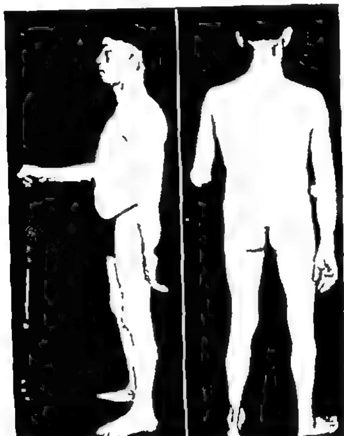


FIG. 320 (No. 40197) The stance of a patient with myeloma, showing the protruding abdomen, the approximation of the ribs to the pelvis, the obliteration of the lumbar curve and the wide base assumed on standing.

Multiplicity is often a striking feature of the fractures. Although in other primary bone tumors repeated fractures are often encountered in the same bone, the occurrence of several fractures in different bones is exceptional. Not infrequently however in cases of multiple myeloma, fractures occur



FIG. 321 (No. 38220) Pathologic fracture through the neck of the left humerus in a case of myeloma. Note the rarefied condition of the clavicle and the mottling of the ribs.

in the same patient in several ribs, clavicle, and sternum. Sometimes both lower and upper extremities as well as the thoracic cage are involved.

Both united and ununited fractures are met with in myeloma. Union of fractures, which is generally slow has been described. In Moore's case, rapid union of the clavicle occurred. In one of Meyerding's cases, in which both femora were fractured, the left united while the right failed to do so. In several of our cases the fracture has healed with the aid of deep x-ray therapy

Spontaneous dislocation of the sternoclavicular joint has rarely been described (Martin, Howard and Crile) Gradual dissolution of a rib may occur so that the mere pressure of the stethoscope is sufficient to fracture it Infraction and crushing of the vertebrae, particularly under strain of lifting, are frequent. The various deformities that arise in this manner have already been referred to.

We think that cases in which fracture is described as preceding the disease as an etiologic factor (Anders and Boston) are subject to reinterpretation. There is no evidence at hand to substantiate such a conclusion

PULMONARY CHANGES

When the thoracic deformity of patients with multiple myeloma is marked, chronic bronchitis and emphysema are common, occurring in 55 per cent of the cases. The prevailing type of bronchial involvement is a diffuse persistent bronchitis of the mucopurulent variety characterized by a productive cough. The debilitated and cachectic condition of these patients, the hypostatic pulmonic changes dependent on their bedridden state and the restricted alveolar ventilation brought about by painful respiration may be considered contributory factors to this bronchial involvement.

Second to bronchitis, emphysema is most frequently observed (Wallgren in five cases, Morse in two cases, McIntyre, Bence-Jones and Dalrymple, Weber and others) Dyspnea and asthmatic attacks are often accompanying features. In these cases, the anginoid pains particularly emphasized by such violent expiratory efforts as sneezing and coughing, cause the patient to breathe shallowly with the chest held in an inspiratory state. Weakening of the alveolar walls consequent to nutritive changes gives rise to emphysema.

Various forms of pleurisy have been reported by Vance, Symmers, Morse, Beck and McCleary McIntyre and Wallgren. In some cases, this has been described as fibropurulent and occasionally as an empyema. At autopsy subpleural nodules or indented fracture deformities of the ribs have been found in association with the pleuritic changes. Pulmonary tuberculosis

has rarely been reported in patients with myeloma.

In these various conditions of the lung, there is a fatal progression—generally to a terminal pneumonia.

NEUROLOGIC OBSERVATIONS

Attacking the bony framework, which otherwise serves as a natural defense for the nervous system, the lesions of myeloma soon produce a number of neuralgic and neurologic symptoms. The most important of these is the paraplegia that follows the involvement of the vertebral column. This together with other forms of neural disturbances is found in about 40 per cent of the cases.

The paraplegia that develops is due to compression of the spinal cord by vertebral tumors most frequently located in the lower dorsal or the lumbar region. The onset is usually insidious, marked at first by weakness of the legs with a tendency to stumbling. There is dwindling sexual appetite, hesitancy in starting the flow of urine and diminished epicritic sensation over the lower extremities. In the next stage, there is exaggeration of the reflexes with development of a positive Babinski sign and ankle or patellar clonus.

In the final stage, there is a flaccid paraplegia with incontinence and the development of decubitus ulcers. The involvement will rarely be unilateral (Meyerding, case 6) In an unusual case reported by the same author (case 9) paraplegia came on after a fall and then gradually disappeared. These rarer forms of receding cord involvement parallel the occasional regressive changes seen in the tumors of the bone in cases of myeloma and are related to vascular changes in the spinal tumor

In a smaller percentage of the cases, the diverse involvement of the skeleton gives rise to neurologic symptoms in other regions. In cases reported by Bloodgood, and Anders and Boston, diplopia developed. In Meyerding's third case, anisocoria and failing vision accompanied a tumor of the skull In a case of Herz, paralysis of a hand was present. In Senator's case, glossoplegia with partial laryngeal and pharyngeal paralysis developed, and Stokvis found difficult deglutition in his patient. There was decided alteration of the voice in a case studied by Anders and Boston.

Wallgren reported cases with tumors in the skull giving rise to thromboses in the intracranial sinuses In Venturi's case, there was thrombosis of the central artery of the retina with complete blindness.

Tumor masses of the ribs give rise to intercostal neuralgia and paravertebral tumors to radiculitis with severe lightning like root pains. Such manifestations are sometimes complicated by herpes zoster

Senator and others, lacking definite anatomic proof that direct impingement by tumor is responsible for many of the lesions of the nerves already described, ascribe to them a toxic origin. Evidence of tumor however is almost always found to account for the symptoms. Ginsburg,* in describing neurologic disturbances of a similar nature observed clinically in ten cases of Hodgkin's disease is of the opinion that they were caused by direct invasion of the nervous system by the proliferating tissue

Although the mind remains clear in most instances, terminal confusion and coma are not rare. Occasionally cases of myeloma occurring in psychiatric patients have been reported (Wallgren)

NEPHROSIS

The changes in the kidney in cases of myeloma are as varied and diverse as the pulmonic changes and are present in a larger portion of the cases (70 per cent)

Hammond† is of the opinion that a chronic nephritis with nonprotein nitrogen retention and a low blood pressure is typical of multiple myeloma. While we have been able to find four such cases (Meyer

* Ginsburg: Hodgkins disease with predominant localization in nervous system, Arch. Int. Med. 39 571 1927

† Hammond. South. M J 17: 483, 1924

ding, two cases, Grant and Brewer and one of our cases) we have also found nephritis with nonprotein nitrogen retention and hypertension in two of our cases (165 systolic and 105 diastolic and 158 systolic and 108 diastolic) Blood pressure determinations in connection with blood chemistry studies sive, nonprotein nitrogen retention type. Gottardi described a similar case which began with intermittent hematuria.

In other cases (Wallgren and our own series) the original clinical diagnosis of the patients underlying condition was chronic nephritis with cardiac hypertrophy In some

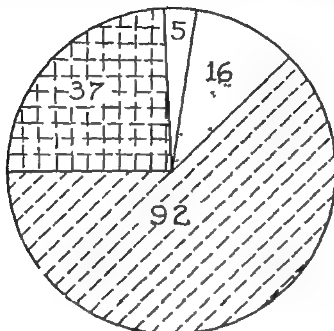


FIG. 322. Nephritis and Bence-Jones bodies in 150 cases of myeloma. The white area (3.3 per cent) indicates an absence of nephritis and Bence-Jones bodies the dotted area (10 7 per cent) Bence-Jones bodies only the crossed area (24.6 per cent) nephritis only and the area of broken lines (61 4 per cent) nephritis and Bence-Jones bodies.

are reported rarely enough to make any conclusions on this point hazardous. It is true that blood pressures in general are low (from 110 systolic and 60 diastolic to 130 systolic and 80 diastolic) but we have been able to collect readings in only some thirty cases.

Clinically the usual occurrence is a nephrosis with albuminuria and anemia, although in one case of our series the patient dated the onset of his symptoms from an attack of acute nephritis with chills and fever anasarca, throbbing headache and hematuria. On admission his nephritic symptoms were of the chronic hypertensive cases, changes of the eyegrounds are reported. In most instances, the report of nephritis is based on autopsy observations. In some cases, the nephritis was described as sclerotic or interstitial, and in others as parenchymatous. Moore and also Wallgren have reported cases diagnosed as nephrosis, or tubular nephritis, and H Weber Senator and others have reported the amyloid reaction in the kidneys.

The gross appearance of the kidneys is usually smooth and white, and microscopic examination shows marked changes in the tubular epithelium, indicating that nephrosis is the primary pathologic process.

However decrease in size and glomerular damage point to a secondary sclerotic process. A small, white kidney is the usual autopsy finding in these cases.

In twenty cases, paraplegia and nephritis are reported in the same patient. In some cases, the nephritis definitely preceded the paraplegia in other cases, the paraplegia was the underlying condition with urinary retention and an ascending infection giving rise to cystitis, pyelitis and renal abscess. In one case, the urinary infection followed paraplegia and could be ascribed to the use of a retention catheter

Metastases have more rarely been demonstrated in the kidney

Great interest is attached to the association of nephritis or nephrosis and Bence-Jones bodies in cases of multiple myeloma. This occurs frequently and we found both in 92 cases, as shown in Figure 322. Bannick and Greene have studied this aspect of the disease.

Decastello, by injection of Bence-Jones bodies into dogs, concluded that a previous nephritis was necessary to their excretion. Stokvis, on the other hand, claimed to have induced nephritis in these animals by similar injections of Bence-Jones bodies. Longcope's work on the effects of foreign protein on the kidney in man would seem to support the contention of Stokvis, that nephritis might thus be brought about.

No single theory for the origin of nephritis has a monopoly on the evidence at hand. While in some cases Bence-Jones bodies are reported in the urine without the ordinary albuminuria expected with foreign protein shock to the kidney still it is possible that by repeated damage to the kidney a dysfunction is brought about. Bell has reported renal insufficiency in multiple myeloma produced by obstruction of the tubules by large numbers of casts apparently due to the precipitation of Bence-Jones proteins Similar findings have been reported by Fishberg. In other cases, amyloid deposits or pyelonephritis have been the cause of renal insufficiency and death due to uremia.

GASTRO INTESTINAL SYMPTOMS

In a disease running a fatal course many terminal complications are to be expected, and certain of the gastro-intestinal symptoms of patients with myeloma are apparently such The diarrhea often met with and the colicky pains described (Meyerding, Wallgren, Bozzolo, Bertoye) are associated with the conditions found at autopsy in most instances of enterocolitis, which, as MacCallum has pointed out, is often a terminal complication in patient with nephritis.

The fatal hematemesis in Bertoye's case, the melena in Wallgren's case 11 and the epistaxis not infrequently observed (Anders and Boston, Bertoye, and in some of our own cases) likewise may be regarded as terminal manifestations associated with a lowered platelet count in marked anemia.

There is an occasional case of outspoken peptic ulcer (Vance, P Weber Wallgren) however which is more difficult to explain. Gastric analyses have been done in only rare instances. These determinations, with few exceptions, show an absence of free hydrochloric acid. To complicate the picture one step further metastases or extensions of the tumor to the stomach and duodenum have been reported. Ulcer formation has not been correlated with tumor formation in these rare instances.

The most frequent gastro-intestinal symptoms are nausea, vomiting and colicky pains. In some cases, there is vomiting without nausea. In cases reported by Meyerding, Wallgren and Jacobson, and in our own series, these gastric disturbances have been associated with compression of the spinal cord, and were perhaps analogous to the gastric crises found in tabes dorsalis (as suggested by Martiri)

The various types of gastro-intestinal symptoms already mentioned are noted in 20 per cent of the cases.

METASTASES

It was long thought that multiple myeloma never involved the internal organs by *metastases, and that if metastasis oc*curred, it was merely as a spreading from one bone to another of a tumor growth primary in a single focus or an original group of foci. Direct extension to surrounding parts was conceded, but when tumor growths were found in the liver and spleen, Lubarsch sought to explain them as separate nodules in hemopoietic tissue, arising independently rather than by metastases.

Metastases to internal organs, however are not at all rare when a careful review of cases has been made. The spleen and liver have been reported as the site for metastases in more cases than have other organs. Growths in the lymph nodes are reported with almost equal frequency

More rarely other organs are affected, the tonsils (Anders and Boston) the thyroid (Fraenkel) the *suprarenals* (*Bechtold*) the ovaries (Herrick and Hektoen)

The metastases, microscopically similar to the original tumor are of the same spherical formation in the gross, but rarely attain a large size (size of a walnut is the largest) When found, they are generally multiple, unless apparently arising by extension from proximal bone.

In general *pulmonary metastases* are not found in myeloma From the point of view of roentgen diagnosis this is exceedingly helpful. The occurrence of subpleural extension of the tumor can be differentiated with due care, and actual *metastatic* growths occurring in the lungs have been reported only by Wieland.

Usually the hemopoietic tissues are the favorite site for the spread of the tumor—the spleen, the liver and the lymph glands predominating Microscopically in the bone marrow growths free tumor cells are found lying within the blood vessels (Fig 325) This has been cited by certain authors to explain the origin of the metastases.

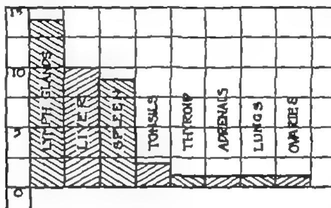


CHART 14 Sites of metastases in cases of myeloma. The left hand column shows the number of cases.

In rare instances metastases may provide the initial manifestations of the disease. This was true of two cases in this series. In one, a woman aged 60 years, there was enlargement of the cervical glands thought to be produced by Hodgkin's disease. After biopsy had established the nature of the disease roentgenograms of the complete skeleton revealed a focus in the ulna. In a second case, a physician aged 55 there had been a feeling of lowered energy prior to the discovery of a tumor of the testicle, which microscopically was of the plasma cell type. Roentgenograms of the skeleton revealed doubtful minute areas of erosion in the skull, but at autopsy there were scattered foci of marrow involvement in the other bones.

Prior to the present decade, these cases

with an initial focus of myeloma outside the skeleton were referred to as examples of extramedullary myeloma. Since the advent of sternal marrow puncture (as a routine laboratory procedure, in such cases) it can be demonstrated that the marrow is nearly if not always, the primary seat of the disease.

BENCE JONES BODIES

Repeated statements in the literature cite the incidence of Bence-Jones bodies as 80 per cent for all cases. Search for the authority or evidence for this statement failed to disclose its source. In the present study excretion of these bodies was reported in 65 per cent of all cases.

On the other hand, a search for an albuminoid substance in the urine of patients with diseases other than myeloma, although infrequently carried out, has shown this substance to be present in a widely varying group of bone and bone-marrow diseases. In 107 cases of diseases other than multiple myeloma in which we could find (either in the literature or in the surgical pathological laboratory of the Johns Hopkins Hospital) a record of a determination, Bence-Jones bodies were found in twenty-six cases. Most of these tests, of course, were made on patients suspected of having myeloma, and the results throw some light on the value of the test in differential diagnosis.

Table 53 has been compiled from the literature and from cases in the surgical pathological laboratory of the Johns Hopkins Hospital.

Despite the fact that twelve different conditions are enumerated in this table the striking feature that all of these diseases involve either the bone or bone marrow is well emphasized. In the case of Fitz, so often cited as an example of Bence-Jones bodies in myxedema, actual perusal of the reference showed the patient to have a tumor of the jaw with sequestra in addition to the hypothyroid symptoms. The case of Coriat in which these albuminoid bodies were found only in the pleural fluid has been



Fig. 323. Bence-Jones protein crystals isolated by Magnus-Levy

referred to by some as miliary tuberculosis, by others as multiple sarcomas. Coriat, in reporting the case did not describe symptoms of either contenting himself with remarks concerning the rare and obscure nature of the patient s condition The evidence would, therefore, seem to indicate that the excretion of Bence-Jones bodies in the urine is specific not for multiple myeloma, but for some pathologic process located in the red marrow bones

The demonstration of Bence-Jones bodies in the urine is indicated by the appearance of a white cloudy precipitate between the temperatures of 50 and 60° C. (sometimes as low as 43 and 46° C.) and on further heating, this precipitate goes into solution at about boiling (90 and 100° C) On cooling, the precipitate reappears. In some cases in which the precipitate does not clear on boiling, *the addition* of a few drops of acetic acid (5 per cent) will dissolve the turbidity If serum albumin is present in the urine, a few drops of acetic acid should be added, the *serum albumin* coagulated and filtered off at boiling, and the foregoing procedure then carried out. By filtering coagulated albumin hot *in the presence* of Bence-Jones proteins, J J Engelfried has been *able to*

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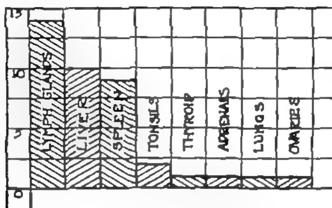


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Despite the fact that twelve different conditions are enumerated in this table, the striking feature that all of these diseases involve either the bone or bone marrow is well emphasized. In the case of Fitz, so often cited as an example of Bence Jones bodies in myxedema, actual perusal of the reference showed the patient to have a tumor of the jaw with sequestra in addition to the hypothyroid symptoms. The case of Coriat in which these albuminoid bodies were found only in the pleural fluid has been referred to by some as miliary tuberculosis, by others as multiple sarcomas. Coriat, in reporting the case, did not describe symptoms of either contenting himself with remarks concerning the rare and obscure nature of the patient s condition. The evidence would, therefore, seem to indicate that the excretion of Bence-Jones bodies in the urine is specific not for multiple myeloma, but for some pathologic process located in the red marrow bones



Fig. 323 Bence-Jones protein crystals isolated by Magnus Levy

The demonstration of Bence-Jones bodies in the urine is indicated by the appearance of a white cloudy precipitate between the temperatures of 50 and 60° C. (sometimes as low as 43 and 46° C.) and on further heating, this precipitate goes into solution at about boiling (90 and 100° C.) On cooling, the precipitate reappears. In some cases in which the precipitate does not clear on boiling, the addition of a few drops of acetic acid (5 per cent) will dissolve the turbidity If serum albumin is present in the urine a few drops of acetic acid should be added, the serum albumin coagulated and filtered off at boiling, and the foregoing procedure then carried out. By filtering coagulated albumin hot in the presence of Bence-Jones proteins, J J Engelfried has been able to

quantitatively precipitate Bence-Jones proteins with sulfosalicylic acid. (Personal communication.)

Although various workers claim to have obtained a substance resembling Bence-Jones bodies from various tissues of patients with myeloma (Jacobson from the blood, Ellinger from ascitic fluid, Martiri from the ribs, etc.) the exact source and significance of the substance have never been proved.

It should be borne in mind, in testing for these bodies in patients with myeloma, that they usually appear late in the course of the disease at first they are present only intermittently and generally are a constant occurrence only in the terminal stages.

Possibly related to the abnormal protein metabolism of multiple myeloma is the frequency of amyloidosis in these cases. This has been emphasized by Magnus-Levy More recent reports on atypical amyloid deposits in myeloma have been contributed by Rosenblum and by Fadden

TABLE 53. BENCE-JONES BODIES FOUND IN THE URINE OF CASES OTHER THAN MULTIPLE MYELOMA

Disease	Reference	No. of Cases
A Bone Diseases		
Metastatic tumors of the bones	Orrum, Bradshaw Boston, Boggs and Guthrie, the authors	9
Multiple sarcoma of the bones	Seegelken, Gilmore	2
Senile osteomalacia	Raeske	1
Polyfibrocystic disease	Groves	1
Comminuted fracture	Campbell with Horsfall	1
Caries of the spine.	Wallgren.	1
Tumor of the jaw	Fitz	1
	Total.	16
B Blood Diseases		
Lymphatic leukemia	Herz, Frohman, Decastello, Askanazy	4
Myelogenous leukemia	Simon, Moore, the authors	3
Chloroma	Weinberger	1
Polycythemia	Pribram	1
Experimental aplastic anemia (in a dog)	Zeulser	1
	Total	10
Total, all cases		26

THE BLOOD COUNT

In cases reported as myeloma all types of blood pictures have been described, ranging from primary or secondary anemia to polycythemia, and from leukopenia to leukemia.

When proved cases only are included in the tabulation, those with the blood picture of leukemia can be set aside under a diagnosis of pseudoleukemia or chloroma. The one case of polycythemia with a red blood cell count of 9 000 000 and a hemoglobin of 102 per cent is not a proved case, although Bence-Jones bodies were found in the urine tumors were shown by roentgen examination in the sternum and ribs and there was pathologic fracture of a rib with pleurisy and nephritis. Pribram, himself was at a loss as to how to classify the case, and unfortunately biopsy was not obtained.

In seventy cases of multiple myeloma with complete blood counts, there was a red blood-cell count of over 4,000,000 in

only 16, or 23 per cent, so that it can be safely said that the predominant picture is that of an anemia. The greater number of patients have an anemia ranging between 2,000 000 and 3,000 000 red cells. In only three cases is there an anemia of the primary type with a high color index and a leukopenia, although in twenty six cases there is a high color index.

Normoblasts have been reported in some cases, and megaloblasts have occasionally been found. There are the usual anisocytosis and poikilocytosis found in a marked anemia.

The white-blood-cell count and its differential count present certain peculiarities. In 100 white-blood-cell counts 70 per cent of the cases are within normal limits 23 per cent show leukocytosis and 7 per cent a leukopenia. The majority of the cases in which there is a leukocytosis range in counts from 11,000 to 15 000 In this respect there is no peculiarity for we would expect to find leukocytosis in patients who so generally suffer from secondary infections and secondary anemia.

The unusual features are in the differential count. In about sixty cases with complete differential count, myelocytes ranging between 1 and 10 per cent were found in fifteen cases and eosinophils from 3 to 5 per cent in five cases. Vaughn* has reported myelocytes as a common occurrence in cases

* Vaughn: Operable Cancer J.A.M.A. 69 1932, 1917



Fig 324 (No 47924) Roentgenogram of large cystic area of bone destruction in the ilium produced by solitary myeloma in a woman aged 39 No other lesions were found at autopsy (Case of Dr E. H. Shannon)

of advanced carcinoma, an interesting point in this connection. Abnormal mononuclears or Türck's irritation phenomena are seen (the authors, Wallgren and others) There is a tendency for the mononuclear elements to increase, a relative lymphocytosis not rarely being present. In some cases, the

Table 54. Plasma Protein Determinations in Multiple Myeloma

Normal Values		*Abnormal Values*	
Author	Protein Grams per cent	Author	Protein Grams per cent
Rowe	6.8	Jacobson	7.8
Case & Hubbard	5.27	Author's case	13.4
Bannick & Greene	7.30	Bannick & Greene	9 00 (Case 2)
	6 00		10.54 (Case 13)
	7.00		
Hewit	6.31	Reimann	10 12
Thannhauser	6.41	Medes (cited by Reimann)	16.0
Author's case	7.0	Johansen	12.14
		Wintrobe & Buell	11 9
		Author's case	11.07

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FIG 324 (No 47924) Roentgenogram of large cystic area of bone destruction in the ilium produced by solitary myeloma in a woman aged 39 No other lesions were found at autopsy (Case of *Dr E. H Shannon*)

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TABLE 54. PLASMA PROTEIN DETERMINATIONS IN MULTIPLE MYELOMA

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	6 00		10.54 (Case 13)
	7.00		
Hewitt	6.31	Reimann	10 12
Thannhauser	6.41	Medes (cited by Reimann)	16.0
Author's case	7.0	Johansen	12.14
		Wintrobe & Buell	11 9
		Author's case	11.07

tumor cells have been reported circulating in the blood (Beck and McCleary Wallgren and Aschoff) The exact identity of such cells, however has not been established. An occasional case of malignancy with tumor cells in the circulation has been reported for other diseases (Schleip in gastric carcinoma with vertebral metastases, Marcus Quennell in sarcoma) Since myeloma cells can be found in the vessels pervading the tumor areas, such occurrences are not remarkable.

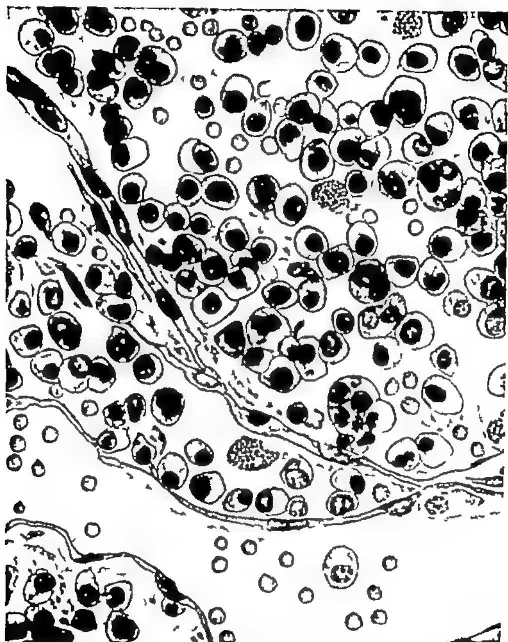


FIG. 325 (No. 1666) Myeloma cells in the small blood vessels. The photograph has been retouched to show accurately the chromatin arrangement in the nuclei, the presence of multiple nuclei and eosinophils.

As a group, these cases present rather a striking blood picture. The high hemoglobin in 38 per cent of the cases is contrary to the ordinary suppressive anemia of malignancy nor is there the aplastic type of anemia bespeaking widespread bone marrow disease

TABLE 55 CALCIUM AND INORGANIC PHOSPHORUS CONTENT OF THE SERUM COMPARED WITH TOTAL PROTEIN CONTENT IN MULTIPLE MYELOMA

Case No.	Total Protein, Gm./100 cc (Normal, 6 5–8)	Calcium, mg./100 cc. (Normal, 9–11)	Inorganic Phosphorus, mg./100 cc. (Normal, 2 8–4 8)	Alkaline Phosphatase units/100 cc.† (Normal, up to 10 units)
1	6 2	10 7	3 7	9
2	7 2	10 7	4	11
3	6 7	12 9	2 8	12
	7 3	12 3	2 6	9
	7	14 7	2 8	7
		14 3		7
4	5 4	11 2	2 5	8
5	6 3	11 2	3	8
6	7 3	10 7	3 6	9
7	6 7	11	2 6	6
8	6 6	[illegible] 9	2 1	6
	5 9	12 3		9
9	6 3	10 5	3 2	8
	7 5	10 7	3 3	9
10	5 4	11	3 2	7
11	7 9	9 7	2 3	8
12	8	9 8	4	14
	9 6	9 3	2 8	7
	8 6	9 7		
13	6	10	2 9	10
14	6 7	12	3 8	9
15	6 6	11 1	2 8	7
16	18 4	10 9	3 6	7
	18 8	10 6		8
	[illegible]	10 4		
17	8 9	11 8	2 1	11
	7 4	10 8		8
18	9 4	12 3	2 8	8
19	7 7	12 9	3 9	7
		12 7	4	12
20	6 2	11	2 4	7
21	7 7	11	3 6	6
22	6 4	18	1 8	10
		18 8	1 9	9
23	6 6	[illegible]	2 6	6
	7 2	10 7	2 3	4
24	10 3	15	2 1	5
		18 8		
		17		
25	6 8	10 6	2 6	
26	8 7	12	2 8	9
	8 6	11		
27	8 7	9 3		
28	10 7	13 3	2 1	4
	10 8	13 3		
	9 7	14	1 1	6
29	6	13 8		
30	[illegible] 21		2 1	
31	13 61	10 6	4 6	
32	16 3	11	3 03	
33	9 1	9 3	3 04	
	10 [illegible]	2 63	9 7	
34	9 93	[illegible]	4 26	
35	8 61	[illegible]	3 78	
	9 37	10	3 47	
36	6 23	[illegible]	5 4	
	7 41	11 9	5 8	
37	6 57	10 5	5	
38	7 73	11 1	3 80	
	7 36			

Snapper I Medical Clinics on Bone Diseases, New York, Interscience Publishers, Inc 1943

† King Armstrong units.

which one might expect. The normoblasts and megaloblasts typifying regeneration and the eosinophils are also contrary to what one expects in metastatic carcinoma. The absence of leukemia is not suggestive of a tumor of hemopoietic tissue.

In most cases, there is a tendency for a displacement of hemopoietic tissue by tumor elements with consequent anemia of the myelophthisic group

BLOOD CHEMISTRY IN MYELOMA

In three instances, myeloma patients observed on the medical wards of the Johns Hopkins Hospital have shown unusual findings in the protein content of the blood

TABLE 56 PROTEIN FRACTIONS IN SERUM AND BENCE-JONES PROTEIN IN URINE OF PATIENTS WITH MULTIPLE MYELOMA

Case No.	Total Protein	Albumin	Globulin	Formol-gel Test	Bence-Jones Protein in Urine
1	6 2	4 4	1 8	Neg.	0
2	6 7	4 8	1 9	Neg.	3+
3	7 2	1 6	5 6	Pos.	2+
	9 3	0 9	8 4	Pos.	3+
4	5 4	3 3	2 1	Neg.	4+
5	6 3	4 9	1 4	Neg.	0
6	7 3	5 4	1 9	Neg.	3+
7	5 7	4 1	1 6	Neg	4+
8	6 6	4 2	2 4	Neg.	0
9	8 3	3 8	4 5	Pos.	0
	7 5	3 3	4 2	Pos.	0
10	5 4	4 2	1 2	Neg.	1+
11	5 9	3 5	2 4	Neg	0
12	8	2 7	5 3	Pos	0
	9 6	3 3	6 3	Pos.	0
	8 6	2 9	5 7	Pos.	0
13	6	4 7	1 3	Neg	0
14	6 7	5	1 7	Neg.	1+
15	6 6	5	1 6	Neg.	2+
16	10 7	2 4	8 3	Pos	1+
	10	2 3	7 8	Pos	1+
	9 7	2	7 7	Pos.	1+
17	8 9	3 7	5 2	Pos	0
	4	3 2	4 1	Pos.	0
18	9 4	4 4	5	Pos	0
19	7 5	4 1	3 4	Neg	0
	7 8	4 7	3 1	Neg	0
20	7 7	4 5	3 2	Neg.	3+
21	5 6	4	1 6	Neg	2+
22	6 2	3 4	2 8	Neg	3+
23	7 7	3 8	3 9	Pos.	0
	7	2 6	4 4	Pos	0
24	6 4	4 2	2 2	Neg.	3+

Snapper I: Medical Clinics on Bone Diseases, New York, Interscience Publishers, Inc 1943.

plasma. The normal concentration of plasma proteins is 6 to 7 per cent. In one case re ported by Perlzweig, Delrue, and Geschick ter and observed in November 1926, the plasma proteins were increased (12.3 to 13.9 per cent to twice their normal value, the pseudoglobulin fraction. The accompanying tables from Snapper show the frequency of abnormal protein fractions in the serum of myeloma patients and in other diseases.

Disturbance of the calcium and phos-

TABLE 57 HYPERPROTEINEMIA AND INCREASE OF PLASMA GLOBULIN IN DISEASES OTHER THAN MYELOMA. COLLECTED FROM 620 ANALYSES OF PLASMA PROTEINS

Diagnosis	Total Proteins 6.5–8.5%	Albumin 4.5–5 5%	Globulin 1 6–2.5%	Fibrinogen 0.25–0.35%
Liver cirrhosis	11 48	3 00	7 59	0 78
Liver cirrhosis	9 04	3 50	5 18	0 36
Chronic nephritis	9 14	3 46	4 76	1 02
Chronic nephritis	9 05	3 70	4 80	0 55
Lymphogranuloma inguinale	8 76	4 02	4 74	
Osteoporosis due to hyperthyroid	9 37	5 28	3 69	0 40
Hypertension	9 11	4 81	3 72	0 [illegible]
Myxedema	8 98	5 42	3 56	
Boeck's sarcoid	8 85	3 97	4 52	0 36
Liver cirrhosis and myxedema	8 77	4 59	3 96	0 42
Polycystic kidney	8 77	4 14	3 84	0 79
Uremia, pyonephrosis	7 85	3 07	4 78	
Liver cirrhosis	8 [illegible]	4 20	3 [illegible]	0 65
Liver cirrhosis	7 54	2 68	4 86	
Boeck s sarcoid	8 22	4 [illegible]	3 27	0 40
Muscle dystrophy	7 40	2 48	4 17	[illegible] 75
Liver cirrhosis	7 03	2 02	4 70	0 31
Liver cirrhosis	7 61	2 04	4 29	0 38
Actinomycosis	8 60	2 34	5 31	0 81
Ovarian carcinoma	8 42	3 25	4 19	0 98
Rheumatoid arthritis	8 54	3 38	4 11	1 05
Bone metastases	7 62	2 05	4 34	0 33
Hemochromatosis	8 30	3 03	5 01	0 35
Lymphogranuloma inguinale	7 61	2 95	4 11	0 54
Liver cirrhosis	7 21	2 78	4 10	0 35

Snapper I Medical Clinics on Bone Diseases New York, Interscience Publishers, Inc 1943

and recently a case has been observed in which a similar increase was found. Determinations of plasma proteins appearing in the literature are listed below

Since the report by one of us on elevat plasma proteins in multiple myelom 1928 the lists of observations abnormal values in the serum globulin h been greatly extended through the ob tions of numerous workers, such as M Levy and Snapper of gl lins occurs in tw cases may either be in th fraction

phorus metabolism may occur in multiple myeloma because of the rapid decalcification of the involved portions of the skeleton. In such cases, the may be dis- clinically because the blood cal not pression of is no eleva the alk of the see tables Snapper) also a fr Sc 69

samples of kala-azar patients in Peking contained more than 1% euglobulin in 8 of the samples more than 4% euglobulin was found.

ROENTGEN OBSERVATIONS

When complete roentgen ray studies are made of the patient with myeloma much is found that is typical of the disease and helpful in diagnosis.

The changes taking place are characteristically distributed in the trunk, in the sternum, in the ribs and in the spine. The skull is usually involved, and when the long pipe bones are affected, there is a tendency for the tumors to be located about the pelvic or shoulder girdle, not infrequently affecting the pelvis. The lesions are characteristically multiple and, in general, confined to the location of the red marrow and thus in the roentgenogram may be termed typically central.

The tumors are bone destructive and show in the pictures as rounded, punched out areas varying from the size of a pea to that of an orange. Sometimes they are more diffuse, giving a rarefied osteoporotic appearance to the roentgenogram, or, when multiple areas have become confluent, resembling mottling.

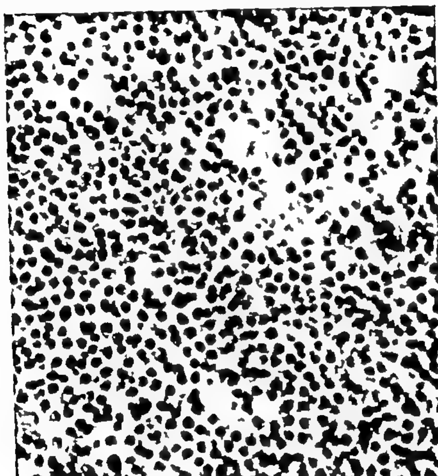


FIG. 326 (No. 47924) Photomicrograph of solitary myeloma from the case shown in Figure 324 Most of the lower ribs show rarefaction and deformity

The ribs are most frequently diffusely mottled, but at the site of the ossified costochondral junctions, there is a tendency for the tumor nodules to stand out more distinctly as areas of bone absorption. Not infrequently tumors about the size of an al

mond are to be seen lying on the ribs, rather than appearing centrally At autopsy they can be found projecting inwardly as subpleural nodules.

Pathologic fractures occur most frequently from the fifth down to the twelfth rib The break is generally not a clean one, but a default through a widened and rarefied area of rib easily overlooked. In some cases, there are noticeable fracture deformities, but not the extreme bending seen in osteomalacia or the multiple globoid enlargements and distortions seen in von Recklinghausen s disease at the site of repeated fractures.

The clavicles may be expanded and rarefied at either the sternal or acromial ends. They are sometimes fractured or subluxated at the sternoclavicular joint. In the sternum, unless lateral views are taken involvement of this bone may be mistaken for mediastinal shadow when the tumor is sufficiently large

Rarefaction and globular tumor formation are both to be found in the spine. Asymmetrical spheroid tumor of a vertebral body may be seen in Fig 327 In the rarefied vertebra, infraction and collapse lead to shortening, disappearance of the intervertebral disks and twisting of the spinal column



Fig. 327 (No. 40917) Roentgenogram of spine in myeloma showing compression of vertebra, and nodular tumor formation of the lumbar vertebra.

with scoliosis. Involvement is most frequent in the lower dorsal and lumbar regions. There is a tendency for more than one vertebra to be involved.

When tumor formation is found in the skull the roentgenogram is of great diagnostic value. Unlike the typical furry thickness of the skull seen in Paget's disease and sarcoma and sometimes in metastatic carcinoma from the prostate, there is no increase in the width of the tables. Multiple punched-out areas are found confined mainly to the frontal and upper parietal regions, generally not as large as in cases of metastatic carcinoma or as mottled as in advanced cases of syphilis of the bone. Large frontal sinuses somewhat like those found in cases of acromegaly have been observed in three or four cases. This is in contrast to the condition found in Paget's disease and leontiasis ossea in which the size is decreased.

The pelvis is sometimes diffusely affected together with the rest of the skeleton, giving the impression that the bone is bloated or puffy with an attenuated structure like edematous tissues.

When the long bones are affected, they show in the early stages, either the multiple punched-out areas, or more rarely an expanded cystic change. Sooner or later however they assume an attenuated appearance, in which there are large areas of rarefaction, rather than expansion within a shell.

Some formation of bone occurs, as is proved by the healing of pathologic fractures and by microscopic examination, yet the roentgenogram rarely shows the formation of new bone in the reviewed cases. This absence of sclerosis about the areas of bone resorption is helpful in distinguishing this condition from metastatic carcinoma in the roentgenogram.

MICROSCOPIC FEATURES

In previous years, the last resort in diagnosis in multiple myeloma was biopsy Today the presence of the disease can be demonstrated by sternal marrow puncture.



FIG. 328. (No. 40917) Roentgenogram of skull showing rarefaction and tumor involvement of the parietal and frontal bones in multiple myeloma.

If one cuts down on the tumor one finds a bone shell of parchment-like thinness, which cuts readily with the knife Sometimes the cortex is entirely absorbed and the spongiosa rarefied. The tumor bleeds freely and is composed of a dark red or gray red mass of gelatinous tissue, the color varying according to the vascularity Very rarely cells that have infiltrated about the periosteum will give rise to distinct extraskeletal tumors (Wallgren, cases 6 and 7)

When cases are selected for study the diagnosis of which rests on a thorough clinical basis, the microscopic observations are generally uniform. The majority of cells in myeloma are round, oval or egg-shaped, 9 to 11 mu in size with an eccentrically placed nucleus averaging 4 or 5 mu. Not rarely a cell containing two or possibly three nuclei is seen and in each nucleus a nucleolus is found. Within the nucleus, sparse chromatin in spokelike arrangement is spaced at the periphery The nucleus is

either globular or more rarely bean-shaped, and has a well-defined nuclear membrane.

These cells, referred to most frequently as plasma cells, do not take the typical plasma cell stain by the Unna Pappenheim or polychrome methylene blue technic; the perinuclear halo is almost always lacking, and the nucleus is slightly larger than the nucleus of the plasma cell.

A type of cell bordering on this description, found in nearly every case intermingled with the larger cells, is a smaller one from about 4 to 6 mu. It slightly resembles the lymphocyte in that the cell is poor in cytoplasm and the nucleus is relatively large in comparison with the rest of the cell. It is globoid and the chromatin, although sparse and of the same mural arrangement as in the larger cells, appears more compact because confined in a relatively smaller space. This more primitive cell is a plasmablast.

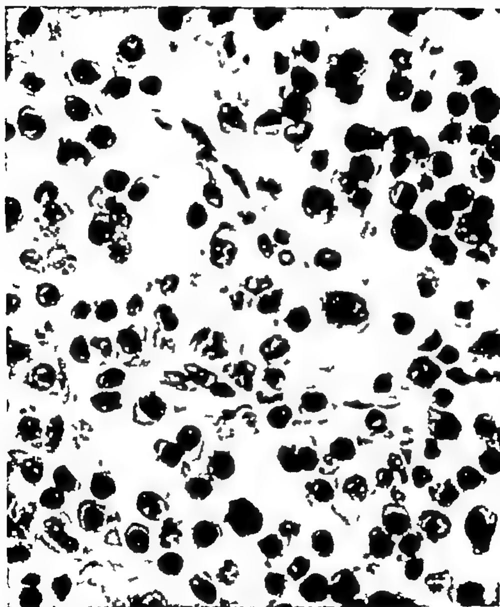


Fig. 329 Typical plasma-cell type of myeloma. Note the uniformity of chromatin arrangement in the nuclei. No 8484.

Between these two types there are all stages of gradual transition and gradation,

giving the impression that they are similar in derivation.

A frequent observation in the sections studied is the occurrence of apparent mitotic figures. The process is seen in many phases, and the frequency of its presence in the larger cells indicates that there is a relationship between this process and the multiple nuclei seen in larger cells.

In regard to the *myeloblastic or myelocytic type of myeloma*, we have repeatedly observed that concerning the *same section* two authorities will differ between these two terms. Ewing in two cases in our series, used the term myelocytic or myeloblastic, while Bloodgood used the term plasma-cell type In running through a series of twenty proved cases in rapid succession, one finds that these two cases do not stand out *especially as atypical* and fit in well with the so-

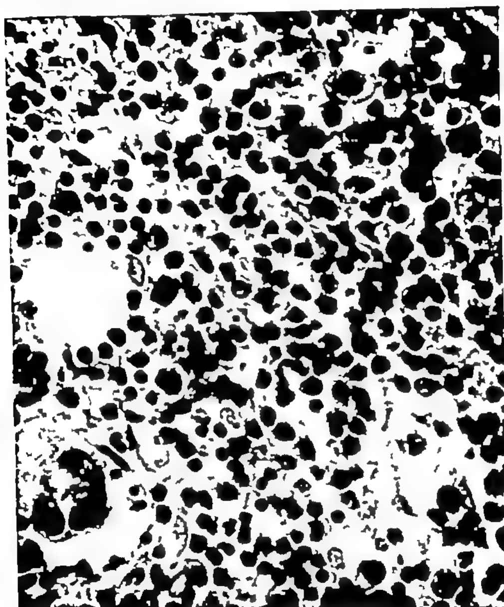


FIG. 330 (No. 38220) Photomicrograph stained with polychrome methylene blue Note the occurrence of giant cells and numerous small cells, which in the picture could be taken for the lymphocytic type of myeloma cell, but which under the microscope are seen to be the typical plasma-cell type.

called plasma-cell type, although superficially the nuclei do not appear to be as typically spokelike in nuclear arrangement. Many authors, in describing such cells in cases of multiple myeloma, are uncertain whether to class these cells in the plasma or myelocytic series, and some of these authors have thought that the apparent difference was due to fixing or staining methods.

In some cases, the differentiation was made on the basis of the oxidase reaction, and in other cases on the Unna Pappenheim reaction for plasma cells (Aschoff, and MacCallum) While the differentiation can thus be made in some cases, often it cannot be made by either oxidase reaction or by Unna Pappenheim stain. Christian, in his study of six cases, believed that the myeloma cell is a transitional form not to be classed as either plasma or myelocytic in type. Wallgren, in the study of thirteen cases, came to a similar conclusion

As a rule, the myeloma tissue is rich in blood vessels. These are thin walled and lined with a single layer of endothelium (Fig. 325) The blood vessels often have about them thin strands of fibrous tissue, although elsewhere in the tumor there is a noticeable lack of intracellular substance with a few fine fibrils here and there There is often profuse hemorrhage into the tumor and in almost all cases, there is a tendency for the tissue to be pervaded by red blood cells. Fat cells, megalokaryocytes and eosinophils are of common occurrence in myeloma tissue and, in most instances, are more numerous at the outskirts of the tumor being the surviving cells of normal bone marrow

The myeloma nodules are only apparently circumscribed, and microscopically it is hard to tell where the tumor begins or ends The growth appears to bring about a direct eating away of the bone, and the cells can be seen surrounding atrophying spicules of bones as if they were responsible for the disappearance of the osseous tissue (Fig 332) There appears to be slight bone formation surrounding the tumor in earlier stages, which would account for the paper thin shell often found. In other cases, the myeloma borders directly on the periosteum or infiltrates into adjacent tissue.

Only in rare instances do myeloma cells enter the circulation, in a manner so characteristic of the myeloblastic, myelocytic or lymphatic leukemias. These cells do not commonly pervade the hemopoietic tissue, such as the lymphocytes crowding into spleen and lymph nodes in lymphosarcoma and lymphoid leukemia, despite the fact that in a small percentage of the cases, metastases are found in the liver and spleen.

Plasma-cell myeloma, associated with plasma-cell leukemia, was reported by Gluzinski and Reichenstein. Their patient had multiple tumors with pathologic fractures of the ribs. Her white count reached 39 400 with 91 per cent of plasmocytes. In a patient reported by Lindh Muller and McNaughton, the spine was involved, the white cell count was 29 000 with 50 per cent plasmocytes. Similar cases have been collected by Patek and Castle.

From a careful study of our own cases, it appears that multiple myeloma is always of the plasma-cell variety In its more undifferentiated state, the tumor tissue may be plasmoblastic and immature cells resembling the lymphocyte predominate. The fact that many hematologists, such as Wintrobe find the plasma cell in myeloma too atypical to be classed with the normal form is an irrelevant matter Such a contention overlooks the important fact that multiple myeloma is a malignant disease and the cells of any malignant tissue are never identical in morphology with their benign counterparts.

Clinically forms of lymphoid, myeloid and monocytic leukemia may resemble multiple myeloma when multiple skeletal tumors are a prominent feature of the leukemia and when Bence-Jones bodies appear in the urine. However these forms of leukemia with pronounced skeletal changes more often involve the skull in the region

of the orbit and give rise to significant changes in the peripheral blood (such as is found in chloroma) See Chapter 20 In the cases of leukemia either the total white-cell count or the differential count or both are altered. More severe suppression of the platelet count frequently occurs with hemorrhagic tendencies. Lymphadenopathy and splenomegaly are likewise more frequently associated with the leukemic state and are rare with multiple myeloma

In some cases of leukemia, the bone involvement is similar to that in multiple myeloma in the roentgenogram. In addition, such cases of leukemia may have Bence-Jones proteinuria and marked hyperproteinemia. Snapper has reported such a case combining the features of leukemia and myeloma and has cited additional cases from the literature. Since several cases of multiple myeloma terminating in plasma cell leukemia have been reported it is possible to look upon multiple myeloma as a subleukemic form of plasma-cell leukemia, in which bone involvement predominates, over changes elsewhere in the hemopoietic system In the ordinary leukemias (lymphoid, myeloid and monocytic) changes in the peripheral blood predominate and osseous manifestations are rare. In plasmocytic myeloma, changes in bone predominate and leukemic manifestations in the peripheral blood, in the spleen and lymph nodes, are rare.

CLINICAL COURSE AND DIAGNOSIS

A brief survey of the more characteristic features of multiple myeloma may serve to unify them into a more composite clinical picture as well as to emphasize some of the striking variations. The cases forming the basis of this survey are tabulated in Table 58

The onset is often insidious with indefinite, wandering rheumatic pains predominantly about the back and loins, or with progressive weakness in the form of general lassitude sometimes marked by a loss of power in the legs adumbrating a gradual paraplegia, sometimes accompanied only by severe anemia The patient's attention is first called to the disease by trauma, spontaneous fracture the discovery of tumor or exacerbated pain brought on by muscular exertion Rarely the initial tumor discovered is metastatic in the lymph nodes or testicle. The complicating features of nephritis or nephrosis gastric disturbances or pulmonic changes may more rarely usher in the disease.

From this initial phase the patients pass on to a period marked by more continuous pains, by increasing deformities with kyphosis, swellings, shortening of stature multiple fractures and paralysis, finally becoming bedridden In some cases, the pulmonic symptoms become more acute and the nephrosis more outspoken with anasarca and progressive cardiovascular changes

Before this stage of advancing disease takes its fatal turn, a remission with temporary decrease or abatement in the intensity of the symptoms will frequently manifest itself In rare instances such a remission may last two three or five years, with or without the benefit of deep roentgen therapy Usually however in a short interval of time final failure sets in with cachexia and anemia. Flaccid paralysis ensues with decubitus ulcers, total incontinence and severe ascending urinary infection Culminating in agonizing pains, the end comes with terminal pneumonia, coma and death.

A patient may present an epitome of this entire range In a case which we studied on the wards there were, on admission, in addition to the marked skeletal deformity with shortening of stature, kyphosis, pathologic fracture and nodular tumors, a bronchitis and emphysema with asthmatic attacks, dilatation of the heart with systolic murmur beginning paraplegia and strabismus, chronic nephritis with hypertension and hematuria, and increased metabolic rate and pronounced anemia. The onset was with an acute nephritis, and during the patient's stay in the hospital, there was marked remission of the disease. Later when the

TABLE 58. MULTIPLE MYELOMA

Pathologic No.	Sex	Age	Duration, mos.	Symptoms	Location at First Examination	Results of Treatment
62724	F	48	2	Limp	Crest of ilium	
62316	F	45		Pain	4th lumbar vertebra	
62056	M	26	1	Swelling and aching left thigh	Femur	
61970	CM	30	6	Pain in hip	Iliac crest	
61948	F	55		Fracture, amputation	Femur lower	Dead few mos.
61848	F	51	2	Pain in coccyx	Lumbar vertebrae	
61550	M	20	3	Low back pain	2nd lumbar vertebra skull	Dead 5 mos.
61400	M	adult	12	Intercostal pain	Spine	Dead 4 yr
60970	M	50	1	Pain in shoulder	Clavicle acromion	
60290	F	50	30	Post traumatic pain, fracture	Spine	Dead 4 mos.
60214	WM				Tibia	Autopsy
59694	M	10	2	Swelling base of neck	1st rib	Well 10 yr
58814	M	55	1	Pathologic fracture	Clavicle	Dead
58582					Scalp	
58316	F	27	2	Pain, swelling	Pubis and ischium	Dead
58298	M	66		Pathologic fracture	Clavicle	Dead 7 yr
57798	F	48	1	Swelling	Skull ribs and pelvis	Dead
57796	F	60	6	Fractures	Skull, ribs and spine	Dead
56806	M	59	2	Severe dull ache in hip, weakness	Ribs and sternum	Dead 7 mos.
55960	F	75	2		Frontal bone	Dead
55910	M	17			Ischium	
55822	M	28	4	Pain in back	Ilium	
55816	M	58	6		Skull and pubic bone	
55610	F	29		Pathologic fracture	Humerus, tibia, skull and radius	
55590	M	17	1	Pain	Pelvis and femur	Well 2 yr
55514	M			Swelling orbital region proptosis	Orbit	
54954	F	50	12	Pain in back	Spine and other bones	Dead 3 mos.
54710	F	60		Pathologic fracture	Humerus	
54606				Swelling, proptosis	Orbit	Dead 5 mos.
54376	M	54	5	Swelling of testicle	Testicle, skull	Dead
54246	F	54	12	Tumor	Skull, pelvis	Dead 1 yr
54268	F	60	10	Pain lower costal area, bilateral, pelvis 6 yr	Spine	Dead 10 mos.
53484	M	45	12	Tumor	Pelvis	
53076	M	55		Swelling of sternum	Sternum	
52468	M	33		Pain in back, weakness	Spine	Dead
52466	M	53		Spinal cord compression	Spine	Dead
52370	F	40	11	Pain	Tibia, os calcis	
52318	M	40	8	Tumor	Mandible	
52316	M	50	9	Trauma followed by "rheumatism"	Nodules in chest scalp and roof of mouth	Dead 1 mo
52240	M	45	4	Weakness of arm	Spine ribs, innominate bones, skull	
51920	M	6	14	Dyspnea		
51832	M	67	30	Tumor fracture	Femur	
51134	F	11	1	Tumor	Skull	
49920	F	52		Weakness 2 yr Back pain 1 yr	Pelvis, spine, ribs, and skull	Dead 8 mos.
49006	M	54	2	Pain, pathologic fracture	All bones	

TABLE 58. MULTIPLE MYELOMA (*Continued*)

Pathologic No.	Sex	Age	Duration, mos.	Symptoms	Location at First Examination	Results of Treatment
47633	M	42	60	Tumor on leg	Ribs, tibia, spine skull pelvis and femur	Dead
46018	M	60	1	Pain loss of weight	Sternum femur and other bones	Dead 2 yr
45948	M	49	4	Pain in back weakness, loss of weight	Spine pelvis and femur	Dead 2 yr
45470	M	17	2	Swollen stiff joints, lumps on head	Ankles, knees and elbows	Dead 10 da
44792	M	66	7	Pain	Humerus	
44740	F	56	12	Pain in back and thigh	Pelvic bone	
43680	M	[illegible]	5	Tumor	Pelvis	Dead 5 yr
42590	M	63		Tumor	Femur	
42358	M	55	1	Tumor	Femur	Living 10 yr
42106	M	45	12		Femur	
41538	M	50		Tumor	Thigh	Dead 6 yr
40816	F	48	10	Tumor	Bones	Dead 0 yr
40814	F	adult		Possible myeloid type of aleukemic leukemia	Tibia and fibula	
40218	F	31	9	Pathologic fracture of vertebra	All bones	
40197	M	40			Skull and other bones	
39914	M	60	5	Tumor	Humerus	Dead 2 mos.
39402	M	6		Tumor incidental finding	Rib	
39006	M	40	6	Tumor	Sternum	Dead 1 yr
38220	F	71	6	Pain swelling in shoulder	Humerus, scapula and ribs	
36826	M	51	8		Skull and femur	
36174	M	adult	96	Pain, swelling	Femur	
35736	M	35	12	Tumor	Femur	Well 14 yr
30225	M	71	12	Pain, pathologic fracture	Femur humerus, clavicle ribs and pelvis	
30129	F	80	12	Fracture	Humerus	
29639	F	72	24	Pain, nodules along all long bones	All bones—66 tumors	
29485	F	37	12	Pain in back, left side and pathologic fracture	Femur and pelvis	
28907	M	55	1	Pain in lumbar region and legs	Ribs, skull and vertebra	
24375	M	19	6	Pain	Scapula	
24295	M	75				
22317	M	54	36		Radius	Dead
19961	M	19	1	Back ache	Vertebra	
16376	M	50			Rib skull and clavicle	
9650	M	35			Rib and sternum	Dead
8184	M	51	18	Pain in shoulder loss of weight	Scapula, ribs, pelvis and skull	
7782	M	38	1½	Pain and tenderness over anterior rib area	Ribs	Dead
7653	CM	56			Rib and femur	Dead
7232	M	27	1	Pain and swelling	Clavicle	
7142	M	66	10	Weakness and loss of weight	Spine chest and pelvis	
1666	F	50	12	Pain, arm and leg	Femur ilium, clavicle, sternum and skull	
47-328	M	52				
47-546	M	64	84	Chest pain	Ribs, vertebra and skull	

patient returned home, there were increasing paraplegia, recurring pain and an aggravation of all symptoms.

With such a complex clinical picture it is not surprising to find the initial diagnosis is often a mistaken one. Lumbago spondylitis deformans, Pott's disease, nephritis, pleurisy tabes dorsalis, Paget's disease, osteomalacia, von Recklinghausen fibrocystic disease, or visceral carcinoma with skeletal metastases are common errors in diagnosis. The symptomatology otherwise misleading, is often clarified by beginning in the skeleton with both osseous and bone marrow destruction and tracing from these two fundamental changes in the skeleton on the one hand, and in the hemopoietic tissue on the other the various disease manifestations of multiple myeloma.

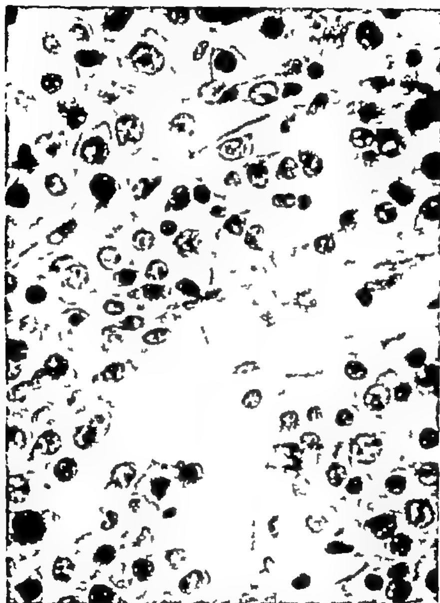


FIG. 331 (No. 28903) Portion of a myeloma rich in stroma. Typical chromatin arrangement of nuclei is again seen.

The tumor formation in the ribs may lead to pathologic fracture or to subpleural nodules and these to hemothorax, pleurisy or even empyema. Again, mere deformity of the ribs with accompanying pain and shal-

low respiration may lead to emphysema and bronchitis. The skeletal deformities in the spine are responsible for shortening of stature and compression of the spinal cord. This neural involvement in the form of radiculitis may give girdle pains and gastrointestinal disturbance, or in the more ominous form of a paraplegia give incontinence and ascending urinary infection with pyelonephritis, the consequent bedridden state resulting in hypostatic pneumonia.

On the other hand, the destruction of bone marrow with anemia is followed by lowered resistance and a tendency to secondary infection. A lowered platelet count occasionally makes these patients prone to hemorrhage and epistaxis. The excretion of Bence-Jones bodies apparently following bone marrow disease goes hand in hand with a chronic nephritis or nephrosis which in turn makes for a terminal enterocolitis.

In this way the disease picture in all its phases, can be shown to have its origin in skeletal tumors.



FIG. 332. (No 7142) Low power field showing the apparent erosion of bone by multiple myeloma.

In lack of a characteristic onset, we must be on the lookout for presumptive evidence of the disease. Of the aggregate of signs and symptoms described, what are the outstanding characteristics which constitute such presumptive evidence?

1 Foremost in the series stands multiple involvement of the skeletal trunk in an adult. Spinal deformity should not be examined without including in that examination the ribs and the sternum. If this had been done in nearly every case in the series studied in which a diagnosis of spondylitis deformans or Pott's disease was made, the correct diagnosis of malignancy at least, would probably have been hit upon, and in all likelihood myeloma itself diagnosed. Deformity of the spine, the parasternal rosary of tumor nodules, bulging and deformity of the ribs—these indicate multiple involvement of the trunk and are characteristic of the disease. Usually such multiple involvement is demonstrable in the roentgenograms. An occasional case may run its entire clinical course with but a single focus in the bones, or the marrow involvement may be clearly demonstrated only at autopsy

2. Occurring less frequently but even more typically peculiar to this disease, is the pathologic fracture of a rib Pathologic fracture of a rib in an adult is ample presumptive evidence for suspecting myeloma. In no other disease does it occur with anything like the frequency found in this condition

3 The outstanding feature detracting from the diagnostic value of Bence-Jones bodies in myeloma is the failure to carry out this test as a routine in bone diseases and tumors of the bone This test is so simple, implying watching for an early precipitate when the usual test for albumin is carried out by slow heating, that it should not be omitted as a routine in diseases of the skeleton. The albuminoid bodies are presumptive evidence of this disease. Their true diagnostic value however will not be known until this test is more often applied in skeletal disease.

4. Although backache and radiating rheumatic pains are commonly found in myeloma, backache is sufficiently widespread clinically almost completely to nullify the diagnostic importance of this symptom. If in realization of the possibility of tuberculosis, metastatic carcinoma, sarcoma or myeloma of the spine, however the clinician elicits a history of early compression of the cord (such as beginning loss of sexual potentia, difficulty in starting urination, or loss of power in the legs) this type of backache, exacerbated by movement, with radiating pains and associated signs of early paraplegia should be suggestive of multiple myeloma.

5 In some instances, an otherwise inexplicable and increasing anemia of the primary type will lead to roentgen study of the bones when the facilities are available. Under these conditions, the possibility of multiple myeloma should be considered.

6. Finally although adequate information is still lacking on this point, the presence of a chronic nephrosis with nonprotein nitrogen retention and low blood pressure should arouse suspicion. In such cases, the urine should be tested for Bence-Jones bodies. The plasma proteins may be markedly increased with inversion of the albumin-globulin ratio, and an analysis of the blood chemistry including such determinations should be made, if possible.

What in itself would not be conclusive assumes through association with similar evidence a diagnostic value of the first order Thus, taken in pairs, triads or collectively as a group, the six conditions of (1) multiple involvement of the skeletal trunk in an adult, (2) pathologic fracture of a rib (3) the excretion of Bence-Jones bodies, (4) characteristic backache with signs of early paraplegia, (5) an otherwise inexplicable anemia and (6) chronic nephritis with nitrogen retention, low blood pressure and high serum proteins are of

cardinal diagnostic importance for multiple myeloma.

The majority of cases of myeloma fit into a syndrome, embracing several of these salient features of the course of the disease which has been described.* Whenever the diagnosis of multiple myeloma is suspected, sternal marrow puncture is indicated to determine the presence of the characteristic myeloma cells.

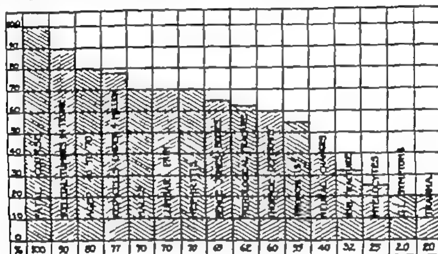


CHART 15 Incidence by percentage of leading symptoms of myeloma

PROGNOSIS AND TREATMENT

The prognosis is uniformly unfavorable, the average duration of the disease being about three years. The longest duration of any proved case is seven years. The duration of the disease appears to be little influenced by treatment, although roentgen therapy may bring about remissions however as we have pointed out, remissions occur spontaneously With no proved case reported as cured, it is evident that palliative symptomatic treatment only is available. Nursing care and orthopedic measures such as traction to avoid unnecessary pain on motion and pathologic fractures is important. When fractures occur the ordinary methods of treatment by fixation may be given as pain is thus minimized and healing often accomplished Narcotics for pain liver diet and tonics for anemia and penicillin inhalations for respiratory complications are helpful. A high calcium and high phosphorus diet with vitamin D should be prescribed.

Among palliative measures, deep roentgen therapy is outstanding Control of pain and acceleration of healing in pathologic fractures have been accomplished under such treatment. In recent years, with improvement in the methods and technic of irradiation, encouraging symptomatic improvement is the rule. It is important that the clinician assume an attitude that is not too pessimistic, since much can be done to add to the comfort and cheerfulness of these patients. Usually the prognosis of the disease can be based upon the degree of ane-mia. Even when this is marked, remission may be obtained with repeated transfusions and judicious roentgen therapy to the major osseous lesions.

Snapper has recently advocated the administration of "stilbamidine" and "pentamidine" in conjunction with a diet low in animal protein for the treatment of patients with multiple myeloma, in individuals in whom there is a widespread bony osteolytic reaction, with normally functioning kidneys. There appears to be some beneficial result

* One of us—(C. F G.) has reported a case of multiple myeloma in which none of these cardinal features were present. (Geschickter C. F Multiple myeloma as a single lesion, Ann. Surg. 91 425 1930.)

in minimizing the excruciating bone pain, but the lesions persist and the disease is not cured, although it may be checked temporarily. Snapper believes that the appearance of granules within the cytoplasm of the myeloma cells is an indication of the specific action of the drugs on these cells. However the toxic effects of the drugs, which include injury of the trigeminal nerve with facial anesthesia, fatty degeneration and necrosis of the liver cells and tubular degeneration and hemorrhage of the kidneys, make their palliative use questionable before roentgen therapy has been attempted for the same results.

SUMMARY

Multiple myeloma is a rare form of tumor causing death and developing in many foci in the red bone marrow of adults. The ribs, spine, pelvis and upper ends of the femurs are most frequently affected and the patients are generally in the sixth decade of life. Clinically, in addition to the rheumatic pains, there are skeletal deformities, leading to pulmonary changes with emphysema and neurologic manifestations such as radiculitis and paraplegia. A nephrosis with nonprotein nitrogen retention and a low blood pressure associated with an albuminous substance in the urine, known as Bence-Jones bodies, is present in from 65 to 70 per cent of the cases. The plasma proteins may be markedly increased. The tumors in multiple myeloma are bone destructive and appear in the roentgenogram as multiple punched-out areas, varying in size from that of a pea to that of an orange. The tumors produce pathologic fractures in 62 per cent of the cases, a rib being the most frequent bone thus involved. Microscopically the tumors are composed of a plasma like cell with an eccentric nucleus containing a spokelike arrangement of chromatin. There is a very scanty amount of intercellular substance. The tumor arises from the marrow tissue, and sternal marrow puncture, to reveal the characteristic plasma cells, is a valuable diagnostic procedure. The disease pursues a fatal course, the average duration of life being approximately three years. Occasional cases live five years or longer but no method for establishing a cure in multiple myeloma is known and no proved cured case has been recorded. Deep roentgen therapy is the most valuable form of treatment in bringing about symptomatic improvement.

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19

Skeletal Metastases Arising from Carcinoma and Sarcoma

Metastases to bone give an extremely variable clinical picture, since the number of different primary tumors responsible for such secondary deposits is large and the type of osseous involvement may be multiple or single, osteolytic or osteoplastic.

The incidence of bone involvement secondary to malignant disease arising elsewhere in the body is extremely difficult to determine. The distribution of such skeletal diseases can be ascertained only by thorough roentgenographic study of the skeleton and multiple samples of bone marrow obtained at the autopsy table. Since their skeletal manifestations often occur late in the disease as part of a generalized picture of cachexia, pain and a bedridden state, a large number of them receive no special study by the attending physician and go unrecorded in the notes of the consultant who managed the operative phase of the disease.

It is the authors impression from clinical observations of the late stages of the disease that extension to bone occurs in nearly 50 per cent of the cases of mammary renal, prostatic and bronchiogenic carcinomas, and is clinically manifest in about 25 per cent of the cases before the termination of the disease. Skeletal metastases from thyroid carcinoma may be nearly as frequent, but we have had less experience with this type of malignancy These are the forms of carcinoma which also metastasize to the lungs. It is now believed by most observers that such skeletal metastases are via retrograde extension through the valveless veins of the intercostal and vertebral systems, as first described by Batson.

Bone involvement is relatively less frequent in gastro-intestinal carcinomas, where the venous drainage is via the portal system and tumor emboli are removed in the hepatic sinusoids. Skeletal invasion is also rare in those types of malignancy in which tumor emboli are screened out by the sinus-

oids of the lymph nodes, such as squamous-cell carcinoma of the skin, of the oral cavity and of the female cervix, and melanomas.

Osseous metastasis, of course, is most common in those cases of mammary, prostatic, renal, thyroid and pulmonary carcinomas, in which treatment is late and ineffective. Speaking in terms of generalities, the duration of symptoms, prior to diagnosis, in such cases is in excess of one year. The interval following treatment to the time that skeletal involvement is manifest is about 18 months, and the duration of life following metastases is one year, giving a total clinical course of three and one-half years.

The outstanding complications which follow skeletal metastases are severe pain, pathologic fracture and compression of important neurologic structures, such as the brain stem, the eye, the spinal cord and the spinal nerve roots.

In the past twenty years, the management of metastatic malignancy to bone has undergone important changes. Prior to this time palliation with narcotics was the chief form of therapy. Modern methods of treatment include orthopedic appliances for pathologic fracture, deep roentgen therapy, castration with the administration of sex hormones, and the addition of calcium in various forms, per os and parenterally. More recently, radioactive phosphorus and calcium have been administered. It is not unusual in the present era of treatment for the patient to survive skeletal metastases by periods of from three to five years, and many of the pathologic fractures can be prevented, if careful management is maintained.

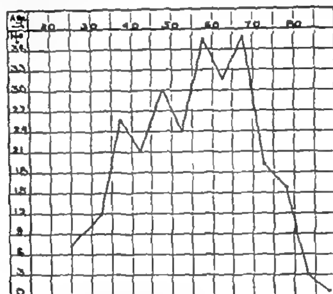


CHART 16. Age incidence of metastatic carcinoma and metastatic sarcoma in 334 cases with secondary involvement of the bone.

CARCINOMA OF THE BREAST

Carcinoma of the breast is one of the most frequent primary tumors metastasizing to bone. A survey of 1 914 cases of mammary carcinoma revealed 903 deaths, 757 of which were caused by dissemination of cancer and 146 from causes other than malignant disease. In 89 (11.8 per cent) cases in which death was due to cancer, lesions of the bone were found prior to death. In addition to these fatal cases, 12 other patients, not yet reported dead, have developed metastatic carcinoma of the bone, making a total incidence of 100 cases (Table

TABLE 59 CASES OF CARCINOMA OF THE BREAST WITH METASTASES TO BONE

Path No.	Color	Sex	Age	Primary Tumor	Location of Primary Tumor	Primary Operation	Location of Metastases	Pathologic Fracture	Interval Between Appearance of Tumor and Metastases	Interval Between Primary Operation and Metastases	Treatment of Metastases	Duration of Life Following Metastases
41894	W	F	40	Cystic adenoma, carcinoma	Right breast	Gland biopsy right axilla	5th, 6th and 7th thoracic vertebrae		27 months	3 months	Radium, 6 Gm. hrs.	Lost
44643	W	F	38	Adenocarcinoma	Left breast	Radical amputation	Spine, ribs		33 months	9 months		Lost
43940	W	F		Adenocarcinoma	Left breast	Radical amputation	Ribs, pelvis, upper end of femur			1st op.: 43 mos 2d op.: 31 mos.		Living after 1 mo.
				Scirrhous carcinoma	Right breast	Amputation of breast						
42718	W	F		Scirrhous carcinoma	breast	Excision of tumor	Pelvis					
41294	W	F	45	Carcinoma	Left breast	Radical amputation	Lower part of lumbar spine, pelvis and hip joints		60 months	34 months	Roentgen rays	Living after 18 mos.
41334	W	F		Carcinoma	breast	Radical amputation	Humerus, clavicle, pelvis		33 months	30 months		Living 24 mos. 1928
40830	W	F	63	Scirrhous carcinoma	Left breast	Radical amputation	4th and 5th lumbar vertebrae, pelvis, sacrum, upper part of femora		73 months		Roentgen rays	Living 9 mos.
40716	W	F	45	Scirrhous carcinoma	Right breast	Radical amputation	3d and 4th lumbar vertebrae, right ilium, right sacroiliac joint			12 months	Roentgen rays (24 times)	Living 12 mos. 1928
40685	W	F	70	Medullary carcinoma	Right breast	Radical amputation	Bone (right leg)					Dead
40636	W	F	63	Scirrhous carcinoma	Left breast	None	Upper end of left femur, lower third of right femur, upper end of right femur		4 months		Roentgen rays	Lived 2 mos. 4 wks.
40368	W	F	47	Scirrhous carcinoma	Right breast	Radical amputation	Skeleton					
40002	W	F	45	Scirrhous carcinoma	Right breast	Radical amputation	Upper end of right femur, ilium	Femur below trochanter	2 weeks		Resection head, neck, right femur x-rays	Lived 13 mos.
39738	W	F	39	Cystic adenoma, carcinoma	Left breast	Amputation of breast	Spine					
39636	W	F	47	Scirrhous carcinoma	Right breast	Radical amputation	2d lumbar vertebra					Dead
39630	W	F	36	Scirrhous carcinoma	Right breast	Radical amputation	Spine		20 months	19½ months	Roentgen rays	Living 10 mos. July 1929
39305	W	F	70	Scirrhous carcinoma	Left breast	Radical amputation	6th dorsal vertebra					
38772	W	F	80	Scirrhous carcinoma	Right breast	Radical amputation	Upper end of right sacrum, right ilium					
38416	W	F	40	Scirrhous carcinoma	Right breast	Radical amputation	10th rib, left, posterior		12 months			Lost
37670	W	F	45	Adenocarcinoma	Left breast	Amputation of breast	Skull, humeri, scapulae, clavicles, femora, all ribs, pelvis		79 months	21½ months	Roentgen rays	Lived 13 mos.
37362	W	F	37	Fibrosarcoma	Right breast	Amputation of breast	4th and 5th cervical vertebrae		3 months	2 or 3 mos.		Lived 13 mos.
37334	W	F	58	Scirrhous carcinoma, left breast	Left breast	Radical amputation	Left ischium, upper third of left femur		40 months	16 months	Lead and radium; Roentgen rays	Lived 9 mos.; Lived 28 mos. plus

37526	W	F	53	Scirrhous carcinoma	Left breast	Radical amputation	Skull, right sacro-iliac joint				Lead and roentgen rays	Lived 13 mos.
37192	W	F	33	Scirrhous carcinoma	Right breast	Radical amputation	Long bones			47 months	Roentgen rays (?)	Lived 9 mos.
37186	W	F	54	Scirrhous carcinoma	Left breast	Radical amputation	Right humerus, right femur ilium, vertebra				Roentgen rays	
36968		F	49	Carcinoma	breast	Radical amputation	Left ilium, left iliac joint, acetabulum, upper third of left femur, upper third of right femur	Left ilium		36 months	Roentgen rays	Lived 12 mos.
36727	W	F	56	Scirrhous carcinoma	Left breast	Radical amputation	8th dorsal, 4th and 5th lumbar vertebrae, ilia, acetabula, ischia, femora				Roentgen rays	Lived 11 mos.
36004	W	F		Carcinoma	Right breast	Radical amputation	6th and 7th thoracic vertebrae			36 months	Roentgen rays	Lived 5 mos.
35575	W	F	36	Carcinoma	Right breast	None	Skull, spine		24 months			Living 6 mos. 1916
35363	W	F	49	Carcinoma	Left breast	Not stated	Spine		36 months	24 months	Roentgen rays	Lived 24 mos.
35420	W	F	54	Carcinoma	Right breast	Radical amputation	Right ilium, upper part of femur 5th lumbar 7th and 10th thoracic vertebrae left femur pelvis			37 months	Roentgen rays	Lived 24 mos.
34980	W	F	43	Scirrhous carcinoma	Right breast	Radical amputation	Left sacro-iliac joint, left ilium, 4th and 6th thoracic vertebrae		[illegible] months	9 months	Roentgen rays	
34396				Carcinoma	Right and left breasts	Amputation of breasts	Upper third of femur	Femur			Exploration, fracture wired	Lived 9 mos.
34100	W	F		Scirrhous carcinoma	Left breast	Amputation of breast	7th dorsal vertebra, cervical vertebrae		6 months	7 months	Radium roentgen rays	Lived 9 mos.
33314	W	F		Carcinoma	Left breast	Amputation of breast	Pelvis			23 months	Roentgen rays	Lived 23 mos.
33060	W	F	41	Scirrhous carcinoma	Right breast	Radical amputation	All lumbar vertebrae, sacrum, pelvis, hip joints		13 months	5 weeks	Roentgen rays	Lived 6 mos.
32758	W	F		Carcinoma	breast	None	Lower end of femur	Femur			Rest in bed	Living 13 mos., 1924
32228	W	F		Cylindroma, carcinoma	breast	Radical amputation	1st lumbar vertebra			56 months	Roentgen rays	Living 19 mos.
31688	W	F	37	Scirrhous carcinoma	Right breast	Radical amputation	Right femur humerus, ischium, left humerus, radius, femur skull cervical vertebrae	(1) left femur (2) right femur			Rest and splints for fractures	Lived about 14 mos.
31650	W	F	44	Scirrhous carcinoma	Right breast	Radical amputation	Right femur left femur skull, ilium, vertebrae	Right femur	9 months	Few days	Roentgen rays Glover serum	Lived 33 mos.
31273		F	48	Carcinoma	Left breast	Radical amputation	2d lumbar vertebra			16 months	Roentgen rays	Lived 9 mos.
30446	W	F	50	Scirrhous carcinoma	Left breast	Radical amputation	2d lumbar vertebra		30 months	4 months	Roentgen rays	Lived 71 mos.
30309	W	F	51	Scirrhous carcinoma	Right breast	Radical amputation	Left ilium			144 months	Roentgen rays	Lived [illegible] mos.
30009	W	F		Scirrhous carcinoma	Right breast	Radical amputation	3d rib, anteriorly		78 mos. plus	72 months	Resection of rib tumor roentgen rays	Lived 29 mos.
29841	W	F		Colloid carcinoma	Left breast	Amputation of breast	Skull, ribs on right side				Roentgen rays	Lived 21 mos.
29331	N	F	50	Carcinoma, inoperable	Right breast	None	6th and 7th dorsal vertebrae, right clavicle, right scapula					
28773	W	F	73	Carcinoma	Left breast	Radical amputation	Sternum		133 months plus	About 133 months		
28440		F	51	Comedocarcinoma	Left breast	Radical amputation	Spine		16 months plus	16 months		Lived 3 mos.

60) or 5.2 per cent of all carcinomas of the breast in this study Many of the patients living to date have not reached the five-year period, and only the future can determine their clinical course.

Metastatic cancer from the breast in bone is a disease occurring in middle or late life. The majority of the lesions occur between the ages of 35 and 55 the extremes in age being 21 and 73 (Fig 333) The cases in the other in the lower end of the radius. With widespread skeletal involvement, lesions in both tibiae have been observed recently and in other cases the bones of the hands were affected.

Prior to 1910 accurate information concerning the location of metastases was gained by necropsy and physical examination. In general, these statistics afforded a trustworthy evidence in bones that were

TABLE 61 INCIDENCE OF BONY METASTASES IN BREAST CANCER

	100 Cases		[illegible] Cases †	
	No of Cases	Percentage of Total	No. of Cases	Percentage of Total
Spine	30	30	12	3.6
Pelvis.	29	29	0	0.0
Femur	22	22	14	4.2
Ribs	13	13	28	8.0
Cranial bones	13	13	9	2 7
Humerus.	6	6	9	2.7
Sternum	4	4	30	9.0
Clavicle	3	3	5	1.5
Scapula	3	3	1	0.3
Radius	1	1	0	0.0
Tibia	1	1	1	0.3
Ulna.	0	0	0	0.0
Fibula	0	0	0	0.0
Patella.	0	0	1	0.3
Bones of hand.	0	0	1	0.3
Bones of foot	0	0	0	0.0

From the Surgical Pathological Laboratory 1930.
† From Sampson Handley Cancer of the Breast and Its Operative Treatment, 1906.

whom skeletal metastases make their appearance note symptoms referable to the affected bones within six to eighteen months, as a rule. In exceptional cases, the interval following radical operation is from five to eight years.

The bones most frequently involved are those of the spine, pelvis, femur skull, ribs and humerus in the order given (Table 61, Fig. 333) While metastases were rarely found in the bones of the forearm and the lower part of the leg,* isolated instances are noted one in the upper end of the tibia and the common site of pathologic fracture, or that were easily accessible at the postmortem table. With the advent of roentgen technic, roentgenograms of the entire skeleton have permitted greater accuracy and have facilitated the study of the incidence of bony metastases in various parts of the skeleton. However many bones, such as the sternum and ribs, can be demonstrated microscopically to be invaded by tumor although the evidence may not appear in the roentgenograms. A comparison of statistics based on the older methods of examination and those of more recent studies which include roentgenologic examinations shows the greater value of the combined methods (Tables 61 and 62)

* Osler W Medical Aspects of carcinoma of the breast, Brit. M. J 1 1 1906 Neal, M P., and Robnett, D A. Generalized osseous metastases secondary to atrophic scirrhus carcinoma of left breast, Arch. Surg. 14 529, 1927

TABLE 62. PERCENTAGE OF CASES IN WHICH METASTASIS FROM MAMMARY CANCER INVOLVES THE MAJOR ORGANS

	Warren and Witham Per Cent	Gross Per Cent	Turner and Jaffe Per Cent	Saegur and Parker Per Cent
Lymph nodes	71.9			
Lungs	58	50	62	65
Pleura	39	51		
Liver	59	48.6		55
Bone	43	20.5	57.1	
Brain		9.4		
Skin	40			
Other breast	13	7.8		
Adrenals	32			44
Ovary		8		16
Spleen				23

SYMPTOMS

Clinically pain of a severe rheumatic character is an important feature. When these metastatic foci localize about the spine, girdle pains and neurologic manifestations are present abdominal pain and pain in the sciatic nerve, numbness of the legs or arms, spastic paralysis or weakness of the extremities. Loss of vesical control and weakness of the rectal sphincters are not infrequent signs.

Often there are pains about the head associated with involvement of the skull, and four cases showed ocular changes, three unilateral exophthalmos and the other bilateral choking of the disks. In addition, metastatic deposits in the extremities themselves often give severe, boring pains, stiffness of adjacent joints and swelling of the affected limb

In the beginning, pain may be so mild and transient that it attracts little notice, and only after more ominous symptoms appear is medical aid sought. The patient may be seized at the onset with excruciating pains and occasionally pain precedes roentgenologic evidence of bony metastases from three to eighteen months.

Pathologic fracture occurred in fifteen of the cases as an early phase of the metastatic involvement. Thirteen were in the femur one in the ilium, and another case revealed multiple fractures of the ribs.

As was pointed out in a previous com

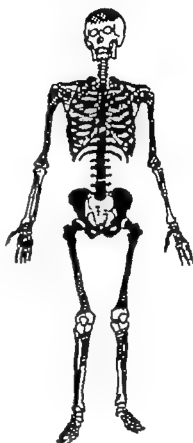


FIG. 333. Distribution of carcinoma and sarcoma with metastases to bone according to skeletal location. The solid black areas indicate the most frequent sites; the checked areas, the common sites· the diagonal lines, the occasional sites, and the white areas, rare sites.

munication, among the malignant tumors of bone the greater number of pathologic fractures (62 per cent) were found in association with multiple myeloma, while other types of neoplastic lesions in bone similarly affected by fracture are, in the order of their frequency cyst of the bone, 45 per cent, giant cell tumor 14 per cent

osteogenic sarcoma, 8 per cent, and Ewing's sarcoma,* 5 per cent.

Warren and Witham found 43 per *cent involvement of bone in spite of the fact* that 113 of 154 cases had axillary dissection with radical mastectomy



FIG. 334 (No. 23091) Roentgenogram of the upper third of a femur showing involvement of the greater trochanter and neck, one of the most frequent sites of *metastases in this bone from car*cinoma of the breast.

As the disease advances and skeletal involvement becomes more widespread, rarefaction of the bones of the spinal column becomes marked with impaction and collapse of the vertebrae.

Patients show great variability in their constitutional response to invasion by the tumor In some cases a rapid progress of the disease is noted with little or no attempt on the part of the body to react, while in others, *with the assistance of various thera*peutic aids, improvement occurs, and the patients are able to live useful lives for several years in spite of the skeletal disease

The blood picture is normal in most cases of early bony metastases the majorit them eventually show secondary ane as the disease progresses. The leuko *count is practically* normal, save for a sl eosinophilia in a few instances—from to four per hundred cells. In the literat an occasional case with bony metastas reported, showing a pseudo-pernicious t of anemia with a color index over 1, a sl leukocytosis, nucleated red blood cells, elocytes and myeloblasts. The ordinary emia of cancer according to Piney † is dependent on the presence of carcino tous deposits in the marrow but on intri changes in this tissue. Blood changes si lating those in pseudo-pernicious ane have always been found in cases in wl metastases have been present for a suffic time to permit hyperplasia of the marr The blood chemistry is normal in most tients An occasional trace of albumi found in the urine, and in three cases Be Jones bodies were isolated. (See Cha 18)

The terminal phases of the disease sl progressive emaciation and anemia, o with much pain when the lungs are volved (nineteen cases) respiratory barrassment with spitting of blood *paroxysms of coughing occur Pleurisy* effusion with cardiac embarrassment later complications.

Internal metastases usually present th selves later than the secondary deposit bone.

ROENTGEN STUDIES

Lesions of metastatic carcinoma of breast which have localized in the bone most often multiple, occurring as a sin focus in about one fourth of the cases. T majority of these solitary *metastases* are the vertebrae or femur but *it is very pr*

* Copeland, M. M., and Geschickter C. F Ewing's sarcoma, Arch. Surg. 20 258 1930.

* Epstein, J Blutfunde bei metastatischer C cinose des Knochenmarks, Ztschr f klin. Med. 121 1896. Houston, T : The Conditions that S ulate Pernicious Anemia, Brit. M J 2 1257 1

† Piney A.: Carcinoma of the bone marr Brit. J Surg. 10 235, 1922–1923.



FIG. 335 (No. 31650) Metastatic carcinoma from breast. Involvement of the greater trochanter neck and upper shaft of the femur The bones of the pelvis on the same side are affected.

able that if such cases were followed to their termination, lesions in other bones would appear

Two types of metastatic lesions are noted in the roentgenograms. The more common one is osteolytic or bone-destructive while the other is a sclerosing or bone-forming process.* The latter is rare in mammary carcinoma, although it is not uncommon in bony metastases from carcinoma of the prostate.

When a long bone such as the femur is involved, the portion affected is usually the proximal end. In the femur the metastases occur most frequently about the greater trochanter and surgical neck (Fig 334) producing destruction of the bone with little evidence of repair There is practically no periosteal reaction. The lesion appears initially as a medullary involvement and subsequently destroys the cortex from within. It is interesting to note that often the focus of tumor in the femur is well above the

Plank, T H. An unusually interesting case J Radiol. 4 347 1923. Ginsburg, S. An unusual case of osteoplastic skeletal metastases Arch. Surg. 11 19 1925



FIG. 336. (No 35420) Mammary carcinoma involving the greater trochanter and upper shaft of a femur with thickening of the cortex below the lesion and evidence of the formation of new bone within the area of destruction.

point of entrance of the nutrient artery * a fact cited by Handley † in favor of lymphatic permeation as a mode of metastases. This will be discussed subsequently



FIG. 337 (No. 40002) Metastatic carcinoma from breast. Roentgenogram of the pelvis and upper third of a femur showing the associated involvement of pelvis and femur which is due to an extension of the tumor from the pelvis along the ligamentum teres.



FIG. 338. (No 31688) Metastatic carcinoma from breast. Roentgenogram of the lower third of a femur showing involvement of the inner aspect of the lower shaft.

Often mottling with increased density of the bone occurs within the area of destruction (Figs. 335 and 336) and thickening of the cortex appears above or below the site of metastasis. This increase in density is found microscopically to be an attempt at repair by the bone, or fibro-ostosis.‡ This reaction is often marked after roentgen therapy over the affected bone.

Bloodgood§ has pointed out that evidence of new bone may be used as a point in differential diagnosis in multiple tumors of the bone. When this formation occurs as mottling within an area of destruction in the bone, it favors the presence of a metastatic process as opposed to the more definitely punched-out areas of destruction seen in multiple myeloma.

When the pelvis is implicated, the heads of the femurs may be involved, because of an extension of tumor from the pelvis along the ligamentum teres (Fig 337) The significance of such an associated involvement will be pointed out later in a discussion of the modes of metastasis.

* Sobotta, J., and McMurrich, J P Atlas of Human Anatomy New York, vol. 1, G. E. Stechert & Company 1927 pp. 1–96.

† Handley, W S Cancer of the breast and its Operative Treatment, John Murray London, 1906

‡ Geschickter C. F., and Copeland, M. M., with Foreword by Bloodgood, J C. Osteitis fibrosa and giant-cell tumor Arch. Surg 19 169 1929

§ Bloodgood, J C Bone tumors, benign and malignant a brief summary of the salient features based upon the study of some three hundred and seventy cases, Am. J Surg. 34; 229 1920.

The entire femur may be involved together with riddling of other bones, or rarely isolated deposits of tumor may appear in the lower third (Fig 338) The humerus, though less frequently affected, shows the same type of destruction either in the head, in the region of the nutrient artery (which is located medially and opposite the attachment of the deltoid muscle) or the bone may be diffusely involved.

Carnett and Howell* have shown that the humerus together with the shoulder girdle is affected more frequently than has been found in the present series. But among the cases studied by these authors, radical operation for the complete removal of the breast was rare whereas in the cases from this laboratory 75 per cent were subjected to the radical operation from 8 to 18 months before metastases appeared In the cases that received radical operation, the greater part of the lymphatic drainage adjacent to the seat of the primary tumor was interrupted, and the likelihood of regional spread was greatly reduced.



Fig 339 (No. 37870) Roentgenogram of the upper third of a humerus with the other bones of the shoulder girdle and ribs, showing punched-out areas not unlike multiple myeloma, in a case of metastatic carcinoma from breast.

The pelvis, vertebrae, skull, ribs, scapula, clavicle and sternum, which represent the other bones usually affected, showed the same medullary destruction with punched out areas not unlike those seen in multiple myeloma (Figs. 339 and 340) The tendency of these areas to become confluent and to be fringed by bone of increased density is fre-

* Carnett, J B. and Howell, J C. Bone metastases in cancer of the breast, Ann. Surg. 91 811, 1930



FIG. 340 (No 37870) Skull showing metastases from carcinoma of the breast simulating multiple myeloma.



FIG. 341 (No 31688) A metastatic breast lesion in the lower end of the radius. A punched-out area in the region of the epiphyseal line and on the medial side of the bone is seen.



FIG. 342. (No 42528) A latent cyst of bone in the lower end of a tibia, which may be confused with a solitary area of metastatic carcinoma.

quent when the involvement of the skeleton is diffuse. In such cases the lack of distortion or bending of the bones, despite the degree of pathologic change is striking. Such distortion is prevented by either the advanced stage of the disease which confines the patient to bed, or by the use of roentgen therapy The age of the patient is responsible for a degree of brittleness of



Fig 343. (No 42108) A solitary focus of multiple myeloma simulating metastatic carcinoma.

the bones which makes fracture rather than bending the rule.

A solitary area of metastatic carcinoma may be simulated by a latent cyst of the bone (Fig. 342) a solitary focus of multiple myeloma (Fig 343) or by the osteolytic form of osteogenic sarcoma (Fig. 344) The latent cyst is to be distinguished from metastatic carcinoma by the distinct signs of ossification present in the bone shell and the thickness and competent defensive reaction in the areas surrounding the walled off cavity The latent bone cyst is nearly always without symptoms, whereas pain and dysfunction of the part occur as a rule with the metastatic lesion.

In the roentgenogram it may be practically impossible to distinguish between multiple myeloma and diffuse metastatic carcinoma Both may be central destructive lesions of the bone which gradually erode the cortex from within outward. Bence-Jones bodies in the urine in cases of multiple my

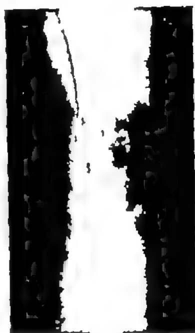


Fig. 344. (No. 37614) Roentgenogram of a femur showing the osteolytic form of *osteogenic sarcoma, not* infrequently confused with the roentgenographic picture of metastatic carcinoma.

eloma, however occur more frequently (65 per cent) than in cases with metastatic carcinoma from the breast (3 per cent)

The osteolytic type of osteogenic sarcoma may produce an area of destruction similar to that in metastatic carcinoma. Such an area shows a greater tendency to be asymmetrically located in the bone and shows evidence of its more rapidly destructive character There is usually a periosteal reaction.

Pathologic Changes

Specimens of the femur and the humerus offer the most valuable information in the interpretation of the roentgen observations, and in analyzing the modes of metastasis.

The humerus is involved principally in the medullary and cortical zones (Fig 345) the medullary cavity in the upper portion of one humerus being practically replaced by carcinomatous tissue. The tumor extended well up into the head of the bone in this case with discrete tumor nodules appearing in the spongy bone just beneath the articular cartilage Below the greater tuberosity the entire cortex is destroyed, while rather substantial bone is found in the region just medialward to this point In the upper shaft of the bone, a cyst with a chocolate-colored wall is seen, the result of old blood.



Fig. 346. (No 40002) A longitudinal section of the upper third of a femur showing areas of metastatic carcinoma from breast just beneath the minor trochanter where pathologic fracture had occurred. In the region of the fovea capitis other deposits are seen.



Fig. 345. (No 37870) A longitudinal section of a humerus, showing involvement by metastatic mammary carcinoma A cyst may be seen in the upper shaft, filled with dark, pigmented, jellylike material.

In one instance, the majority of the deposits of tumor were found in the upper portion around the greater tuberosity and beneath the articular cartilage interrupted by a rather well preserved area of spongy bone. Beneath this area of spongy bone, further down in the shaft, the medullary cavity was found to be filled with tumor tissue the vertebrae in this case also showed focal deposits

The femur often showed metastases in the head and in the region of the greater trochanter with extension into the shaft. In one case a pathologic fracture had occurred just beneath the lesser trochanter at which point tumor was found. In the region of the fovea capitis, another cellular deposit was found (Fig 347) extending beneath the articular cartilage down to the greater trochanter the distance having been much shortened by telescoping of the head on the neck. Other femurs showed less extensive deposits in these same areas. The microscopic examination of sections taken from various points in these bones revealed de-

struction of the spongy and cortical bone by direct contact with tumor cells and to a lesser extent by the activity of the osteoclasts absorbing spicules of dead bone. Regardless of how the tumor cells reach the skeleton, the progress in the bone seems to be via the medullary cavity and the haversian canals, beginning in the areas of red marrow

focus. In cases in which roentgen therapy has been given with beneficial results, microscopic analysis of the affected bone reveals a marked increase in the fibrous tissue reaction and a transformation of this tissue into bone. Cancer cells can be seen crowded between the fibrous strands (Fig. 350)



Fig. 347 (No. 40002) Low power photomicrograph of an area in the region of the fovea capitis taken from the head of the femur depicted in Figure 346 Note the infiltration by epithelial cells from above downward and the area of fibrous tissue reaction below the tumor invasion The joint cartilage is intact on either side of the tendinous attachment.

Abundant evidence is found microscopically to show the capacity of bone to react by direct transition of fibroblasts to osteoblasts in building osteoid tissue. By this method the bone protects itself from further invasion and rebuilds that part already destroyed (Fig. 349) Areas of fibro-ostosis (a reaction to the invasion of cancer) are seen, with strands of fibrous tissue being transformed into osteoblasts and osteoid tissue, bordering on small nests of epithelial cells distributed throughout the reactive

Treatment

In patients with primary carcinoma of the breast, the rate of dissemination of the cancer expressed by the interval between the first appearance of the tumor or the primary operation and the subsequent metastases, throws some light on the results obtained by irradiation or by resection of the affected bones.

For purposes of analysis, the patients have been divided into the following groups (1) those who first had a radical amputation of the breast, (2) those who

had only simple amputation of the breast or local excision (3) those on whom no operation was performed but instead received various forms of palliative treatment.



Fig. 348 (No 40002) Photomicrograph showing nests of epithelial cells from breast cancer in a fibrous stroma with occasional small spicules of old bone undergoing destruction by direct contact with tumor cells.

In group 1 there are 74 patients with radical amputation of the breast, showing subsequent metastases to bone. The average interval between the appearance of the primary tumor and the first evidence of metastases to bone was 32½ months. In a few exceptional cases not included in this average, lesions of the bone developed at intervals as late as from 9 to 20 years. If these exceptional cases are omitted, *the time between radical removal of the breast and metastases averages 30 months.* The tumors in the patients in group 1 were principally of the scirrhus type. Microscopic examination showed scirrhus carcinoma, 52 cases; medullary carcinoma, 4 comedocarcinoma, 3 adenocarcinoma, 3 and gelatinous carcinoma, 1 with 11 unclassified.

Group 2 is represented by 18 cases with a *simple* amputation of the breast or local excision. *The average interval between the appearance of the primary tumor and bone metastases was 29.1 months* On microscopic examination the histology of the primary tumors in this group was unclassified, 7 scirrhus carcinoma, 6 adenocarcinoma, 3 gelatinous carcinoma, 1 and adenocarcinoma, 1.

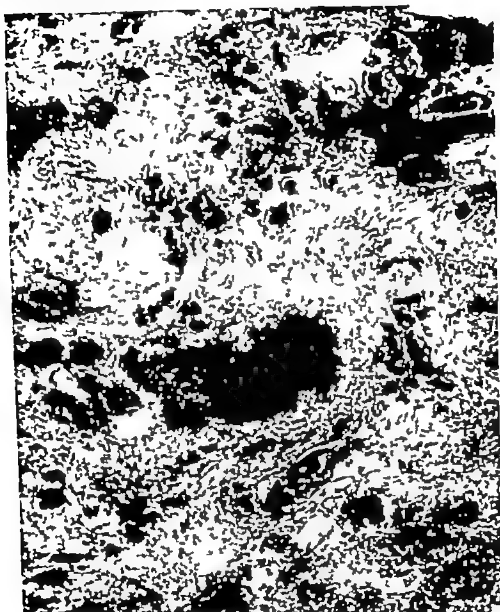


FIG. 349 (No. 12761) Photomicrograph showing areas of fibro-ostosis with strands of fibrous tissue, osteoblasts and osteoid tissue bordering on small nests of epithelial cells from breast cancer

Group 3 or the inoperable group, contained 8 cases. The interval between the appearance of the primary tumor and the metastases ranged between 1 and 24 months. *The average was 12 months*

Using 200 kilovolts and 20 or 30 milliamperes, filtered through a combined 0.50 millimeter copper and 1 mm. aluminum filter and 50 cm. focal distance the lesions are best irradiated in divided doses of 200 roent

gens each. A total of 1000 roentgens over each lesion may be given through a single portal of treatment. If further treatment is



FIG. 350 (No 34100) Photomicrograph showing the effect of roentgen therapy on the structure of the bone invaded by breast cancer Note the healing bone reaction (fibro-ostosis) Cancer cells can be seen crowded between the fibrous strands.

indicated, the foregoing procedure is repeated after a free interval of three months.

While some of the treatments were at other clinics, in the majority of instances the treatment was the equivalent of that given here making the therapy fairly uniform in the various cases.

In group 1 those patients treated radiation after the appearance of met lesions of the bone had an average quent duration of life of 18 months patients survived the metastases for 4 71 months, respectively Among thos irradiated, the duration of life afte tastasis averaged 11½ months.

In group 2, the average duration of persons with metastases who received

gen treatment was 16¼ months as compared with 12⁹⁄₁₆ for those who did not receive irradiation

In group 3, the patients who received irradiation lived 10 months and those who did not receive irradiation, 7 months.

Statistics on the various other tumors metastasizing to bone show that the duration of metastases is essentially the same as in the aforementioned cases.

Resection of the affected part apparently had no effect on the duration of life but gave relief from excruciating pain experienced in the diseased bone.

A number of observers report favorable results from roentgen therapy in metastatic carcinoma of the bone Irradiation is effective both in relieving pain and in accelerating repair in the affected skeleton, apparently reducing the invasive powers, at least temporarily of the cancer In this series of cases, many patients were relieved of pain for varying intervals of time and in twelve cases marked formation of new bone with repair of pathologic fracture was noted and ability to use the affected part was restored.

Modes of therapy other than skeletal irradiation have proved of value in the management of these cases. Castration with mineral and hormonal therapy has extended life about 1 year (average) beyond irradiation alone. Numerous observers have reported beneficial results in from one-third to one-half of the cases with skeletal metastases following roentgen castration in women who have not yet reached the menopause. Daily injections of testosterone proprionate, in doses of 50 mg., given intramuscularly combined with the administration of calcium diphosphate, with vitamins C and D have resulted in the healing of ununited fractures in some hospitals when no deep roentgen therapy was available. The authors have found oil soluble calcium, in the form of calcium duodecyl phthalate, particularly valuable for parenteral administration in these cases.

Levin, I. The prognostic and therapeutic significance of skeletal metastasis in cancer of the breast, Ann. Surg. 65 326, 1917 Kelly H. A., and Fricke R. E.: Problems in treatment of carcinoma of the breast, Surg. Gynec. Obst. 38 399 1924



FIG. 351 (*Top*) Metastasis to ilium and acetabulum in a case of mammary carcinoma. (*Bottom*) Diffuse metastasis to the pelvis and upper femurs from mammary carcinoma. Partial osteosclerosis has occurred after repeated irradiation.

TUMORS OF THE GENITO-URINARY TRACT

Malignancy of the genito-urinary tract is a frequent source of skeletal metastasis. Carcinoma of the kidney tumors of the adrenal and testicle and carcinomas of the prostate are the most common primary sites.

Renal Carcinoma

The great majority of so-called hypernephromas are primary in the substance of the kidney and are carcinomas of renal epithelium rather than misplaced adrenal

tissue.* These tumors arise from the secretory portion of the kidney which forms in the embryo from a cap of undifferentiated mesodermal tissue (the so-called nephrotome). Grawitz,† in 1879 was one of the first to describe such a tumor and in 1898 the term hypernephroma was applied to the neoplasm by Birch-Hirschfeld.‡

There is a feeling among pathologists that the metastases of hypernephroma have a special predilection for the bones, but from an investigation of the literature it is difficult to form any definite idea as to the incidence of osseous involvement.

Among the 63 persons affected by hyper

TABLE 63 CASES OF SO-CALLED HYPERNEPHROMA WITH METASTASES TO BONE

Path No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
46373	W	M	40	Hypernephroma	Right 6th rib		Irradiated	
42906	W	M	55	Hypernephroma	Upper end of right humerus	Humerus	Irradiated, resection of upper end of humerus	Living 22 mos.
42704	W	M	26	Hypernephroma	Left ilium		Irradiated, exploration	Living 3 mos.
38224	W	M	53	Hypernephroma	Bones of foot		Excision of part of tumor	Living 6 mos., 1926
37068	W	M	62	Hypernephroma	Upper third of right humerus		Irradiated, amputation of right arm	Living 7 mos. 3 days, 1926
36524	W	M	66	Hypernephroma	2d, 3d and 4th right ribs, 6th thoracic and 3d lumbar vertebrae	2d, 3d and 4th right ribs	Supporting cast for back	Lived 6 mos.
35762	W	M	52	Hypernephroma	Lower end of right femur	Femur		Lived 9 mos.
34512	W	M	48	Hypernephroma	Tarsal and metatarsal bones of left foot		Exploration, amputation of left foot	Living 6 mos. 1924
35416	W	M		Hypernephroma	Upper end of right femur	Femur		
34362	W	M	56	Hypernephroma	Upper end of right humerus		Amputation of right arm	Living 6 mos. 1921
32074	W	M	40	Hypernephroma	6th right rib		Irradiated, biopsy	
31587	W	F	52	Hypernephroma	Upper end of left femur, left ischium	Femur	Resection of head of femur, bone graft	Lived 10 mos.
30953	W	M		Hypernephroma	4th lumbar vertebra, right sacro-iliac joint, right ilium, skull (parietal region)		Irradiated, erysipelas and prodigiosus toxins (Coley's)	Lived 3 mos.
30631	W	F	60	Hypernephroma	Skull, right temporal bone, left parietal bone		Radium	Lived 24 mos.
29485	N	F	37	Hypernephroma	Upper end of femur	Femur		
29461	W	F	55	Hypernephroma	Midshaft of right humerus	Humerus	Amputation of right arm	Lived 18 mos.
29397	W	M	28	Hypernephroma	All the lumbar vertebrae, all dorsal vertebrae, 3d cervical vertebra, 3d left rib, shaft of both humeri, upper end of femora	Lower end of femur	Hibbs operation	
27964	W	M	30	Hypernephroma	Head, shaft, left humerus		Radium	Living 78 mos. 1927
6930	W	M		Hypernephroma	Humerus		Operation (?)	
6299	W	M	63	Hypernephroma	Left sternum, upper end of femur, ribs	Femur		
2280	W	M	48	Hypernephroma	Femur, humerus, dorsal vertebrae	Humerus		
1415				Hypernephroma	Head of tibia			

* Gibson, A., and Bloodgood, J. C. Metastatic Hypernephroma with special reference to bone metastases, Surg. Gynec. & Obst. 37 490 1923.

† Grawitz, P.: Ueber maligne Osteomyelitis und sarkomatöse Erkrankungen des Knochensystems als Befunde bei Fällen von perniciöser Anämie. Virchows Arch. f. path. Anat. 76 353, 1879.

‡ Birch-Hirschfeld, F. V.: Sarkomatöse Drüsengeschwulst der Niere im Kindesalter. Beitr. z. path. Anat. u. z. allg. Path. 24 343, 1898.

nephroma recorded in this laboratory there are 22 instances (34.9 per cent) with metastases to bone (Table 63) The age incidence ranges between 21 and 81 the peak of incidence is about the sixth decade. The bones usually affected in the order of their frequency are humerus, spine, femur pelvis, ribs, bone of foot, skull and sternum (Table 64)

TABLE 64 INVOLVEMENT OF THE BONE IN TWENTY TWO CASES OF HYPERNEPHROMA

Bone Involved	No. of Cases	No. of Tumors	Right	Left	Undetermined Side
Humerus					
Location (?)	2	3		2	2
Upper third	4	4	3	1	
Shaft	2	3	1	1	1
Femur					
Upper third	4	4	1	2	1
Middle third	1	1	1		
Lower third	1	1	1		
Spine					
Location (?)	1	1			1
Cervical	1	1			
Thoracic	3	13			1
Lumbar	3	7			
Ribs	5	6	2	1	2
Pelvis					
Ilium	2	2	1	1	
Ischium	1	1		1	
Sacro-iliac joint	1	1	1		
Bone of foot	2			1	
Skull	2	3	1	1	1
Sternum	1	1			
Tibia	1	1			1

SYMPTOMS

The lesion of the bone may be the first indication of the presence of the tumor as illustrated by the following case report (Fig. 352)

A white man, aged 55 while in France 11 years previously had an attack of arthritis in the right shoulder which lasted one month, in addition, the left knee both ankle joints, the wrists and the right elbow joint were involved. Following much needed dental work, the arthritic symptoms disappeared except during changes in the weather when they continued to be present in the right shoulder

Twenty months before presenting himself for examination the patient began to have definite pain about the head of the right humerus, with slight limitation of motion in the right shoulder ten months later

A roentgenogram was made in March, 1929 which showed an area of destruction of the upper shaft of the humerus just below the head, about the size of a silver dollar mostly on the outer aspect of the humerus. In June July and September 1929 other roentgenograms were made showing the progressive nature of the destructive lesion. The first evidence of the pathologic fracture was noted in the roentgenogram made in 1930 (Fig. 352 A) associated with a fair-sized tumor of the soft parts. Roentgen therapy had been administered in adequate doses on four occasions with some slight remission in the excruciating pain, but with no great relief Considerable morphine was needed to allay the patient's suffering Other bones in the body were examined but no significant defects were made out, nor were there symptoms suggestive of other lesions in the skeletal framework. Repeated examinations of the urine and of the blood revealed nothing abnormal.

In January 1930 at a neighboring hospital, aspiration of the *shoulder* was done and only blood obtained. In May 1930 the diseased head of the right humerus (Fig 353) was resected and on microscopic examination (Fig but no evidence of any lesion could be made out.

The patient died with metastasis to the liver and spine 5½ years after the onset of symptoms.



Fig. 352. (No. 42900) (A) roentgenogram of the upper end of a humerus showing marked destruction in the region of the surgical neck and upper shaft from metastatic hypernephroma. (B) roentgenogram showing the progressive nature of the metastatic lesion in the head of a humerus, taken three months after (A) (C) the complete destruction in the region of the surgical neck and the resultant pathologic fracture. This roentgenogram was taken about nine months following (A)

354) proved to be the seat of a hypernephroma. Operative recovery was uneventful, and before leaving the hospital the patient had practically abandoned the use of morphine with complete relief from pain. Following the diagnosis of hypernephroma microscopically a special examination was made of the kidneys,

Of those patients suffering with metastatic hypernephroma pathologic fracture occurred in 10 (45.5 per cent) 6 times in the femur 3 times in the humerus, and in 1 instance multiple fractures of the ribs were found. Most of the fractures occurred in the

upper third of the long bones. In one instance pathologic fracture was the first symptom referable to the disease.

As in metastases from the breast, the constitutional response of patients with metastatic hypernephroma of bone is variable. Pain of a rheumatic character is a leading symptom. With spinal involvement many neurologic manifestations may be present. The blood picture eventually shows a secondary anemia, and the patients decline in weight, suffering from progressively severe pains in the various bones affected. In three cases, the urine showed Bence-Jones bodies.

ROENTGEN STUDIES

The lesions in the roentgenogram may be single (Fig. 352) or multiple (Fig. 355) and located in one or more bones. In thirteen cases (59 per cent) the secondary deposit was found as a single focus in the majority of these cases it appeared in a long bone.

It is noteworthy that many of these lesions are at the site of the nutrient vessels (Fig. 356) as well as in the head of the humerus (Fig. 352 (A)) and femur. There may be an associated lesion of the pelvis (Fig. 355 (A)). There is no evidence in bony metastases from hypernephroma of any marked attempt at fibro-ostosis or formation of new bone within the area of destruction. The earliest sign of involvement is always a distinctly medullary defect which destroys the cortex from within, with little or no expansion. Although the growth readily extends into the soft parts, periosteal reaction is the exception. In many instances, the viscera have not been invaded. It is the impression in this laboratory that with small local growths of the tumor in the kidney there is a greater tendency toward dissemination to the bone, whereas larger local proliferations of the tumor are less likely to show skeletal involvement.

The differential diagnosis from the standpoint of roentgenology is similar to that of metastatic lesions of the bone in general, which has been detailed under carcinoma of the breast. In contrast to metastatic tumors from cancer of the breast, *lesions of the bone in hypernephroma* show a greater tendency to occur as a single focus and to be osteolytic.



FIG. 353. (No. 42906) A gross specimen in longitudinal section showing metastatic tumor involvement from hypernephroma in the region of the surgical neck of a humerus, with extension into the epiphysis, and total destruction of the cortex but no involvement of the joint cartilage. Note the subperiosteal invasion.

PATHOLOGY

The gross appearance of the tumor is well exemplified in Figure 353. The growth al

ways has a characteristic brownish yellow color flecked with red. When seen in the head of a long bone, there is marked destruction of the cortex with diffuse involvement of the medullary cavity and the spongy bone of the epiphysis. The cartilage of the joint does not seem to be affected, but there is often evidence of a pathologic fracture with some invasion of the muscle. Studies of the muscle taken at points some distance from the site of invasion by the tumor reveal no tumor cells. This type of tumor occurring as a single focus lends proof to the embolic theory of metastases.

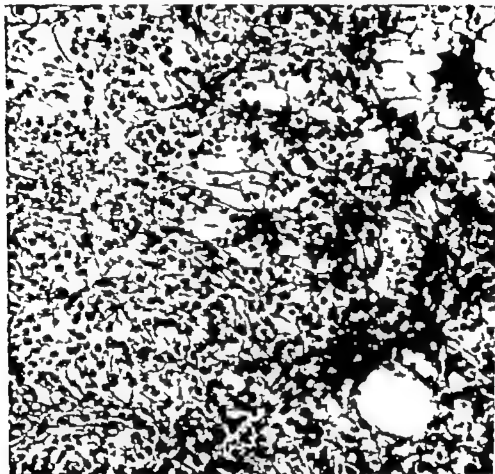


FIG 354. (No. 42908) Photomicrograph of the tumor depicted in Figure 353.

the tumor pushes up beneath the periosteum extending through cortical bone, from the medulla.

In the medullary cavity in many cases, little deposits of brownish tumor can be seen. The tumor tends to grow by a confluence of rounded lobules. Where the shaft is involved at the site of the nutrient vessels (Fig 336) there is destruction of the cortex with tumor in the subperiosteal area, and at the attachment of the deltoid muscle which exerts a tensile influence on the bone,

Further evidence is found in the literature to substantiate this mode of invasion of the bone. Albrecht* reported a case in which there was a single lesion noted in the scapula four years after nephrectomy for hypernephroma. Ten years later following resection of the scapula, the patient was still well. On the other hand, permeation of the lymphatics by tumor cells is undoubt

Albrecht, P A study of the clinical and pathological anatomy of hypernephroma, Arch. f. klin. Chir 74 1073, 1905.



FIG 353 (No 29397) Multiple foci in the skeleton occurring in metastatic hypernephroma. (A) roentgenogram of the upper end of a femur showing metastatic involvement with an associated lesion in the adjacent pelvis and a slight tendency toward the formation of new bone within the destroyed areas. (B) tumor invasion of the upper shaft and head of a humerus. (C) destruction of the lumbar vertebrae with practically no tendency toward the formation of new bone within the destroyed areas.

edly a mode of progression in this tumor in some instances.

The microscopic picture as seen in Figures 354 and 357 is typical of the ordinary structure of hypernephroma of the renal type. The tumor cells have a small, dense eccentric nucleus and a moderate amount of foamy or granular cytoplasm. The stroma is extremely vascular There apparently is little tendency on the part of the bone to wall off the tumor In a few areas there are spicules of old bone being destroyed by direct contact with the tumor cells. The cells are granular or foamy and contain

LeCount, E. R. Report of a case of malignant hypernephroma, Tr Chicago Path. Soc. 5 82 1901-1903. Bierring, W L., and Albert, H : Secondary manifestations of hypernephromata, J.A.M.A 43 234 1904

granules of lipoid. The cytoplasm is usually remarkably clear Its amount and clearness of the cytoplasm depend on the grade and rapidity of the growth The more malignant growths have a relatively small amount of granular cytoplasm



FIG. 356 (No 29461) A metastatic hypernephroma in the humerus at the site of the nutrient vessels showing marked destruction of the bone with expansion

TREATMENT

In this group of cases of hypernephroma with metastases to bone it has been difficult to follow many of the patients, but the data at hand point to the fact that irradiation alone offers as much for the prolongation of life as does surgical intervention alone or surgical measures combined with roentgen or radium therapy (Table 63) One patient (No 27964) who was treated by radium therapy was living 76 months after the first symptoms of the tumor Aside from the prolongation of life, however there is the problem of pain. In instances in which one metastatic lesion is present or in which a bone with multiple lesions is easily accessible to surgical measures, and in which the condition of the patient is such that operation may be performed, much relief from pain can be given by resection of the affected part. One important factor in the treatment of this tumor by irradiation is the relatively resistant character of hypernephroma to irradiation.* Unless roentgen therapy in keeping with the dosages discussed under carcinoma of the breast is available, the patient should be referred elsewhere for treatment. The authors have been able to control pain in metastatic hypernephroma with injections of oil-soluble calcium. The preparation used is the calcium salt of duodecal phthalate. One hundred milligrams of the preparation are given every other day intramuscularly The pain and spasm is relieved but the growth of the malignant nodules is not controlled. The corresponding salt, using radioactive calcium, should give better results.

TUMORS OF THE PROSTATE

Carcinoma of the prostate with metastases to bone is of frequent occurrence, as reported by those clinics and laboratories where considerable genito-urinary material is seen.† Among 1,020 cases of cancer of the prostate in the Brady Urological Institute‡ and 20 cases recorded in the Surgical Pathological Laboratory 134 instances of metastases to the bone were found. It must be pointed out, however that roentgenograms have been made in only about 50 per cent of the total number of cases, and in only 25

* Dresser R. Metastatic manifestations of hypernephroma in bone, Am. J Roentgenol. 12 342. 1925.

† Bumpus, H. C. Roentgen rays and radium in the diagnosis and treatment of carcinoma of the prostate, Am. J Roentgenol. 9 269 1922. Blumer G. A report of two cases of osteopathic carcinoma of the prostate with a review of the literature Bull. Johns Hopkins Hosp. 20: 200 1909

‡ The authors were indebted to Dr Hugh H. Young for the privilege of studying this material

per cent of this number were secondary deposits in the bone found.

The bones most frequently involved are those of the pelvis and vertebrae particularly the lumbosacral region more rarely the femurs and in two instances the lower end of the tibia and the skull.

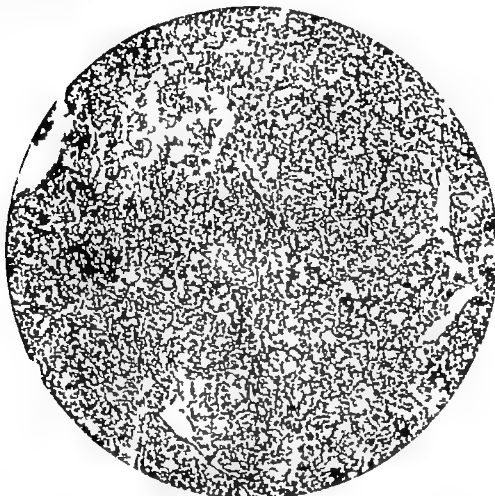


FIG 357 (No. 29461) Photomicrograph of the tumor shown in Figure 356 Note the typical structure of hypernephroma cells with an occasional blood sinus. The cytoplasm of the cells is quite clear and there is little evidence of stroma.

The age incidence is well beyond 50 years (Table 65) These patients showed obstructive urinary symptoms and enlargement of the prostate at the time the metastases were noted. Many patients following prostatectomy for extremely small carcinomas, verified by subsequent pathologic examination, develop osseous lesions a few years later

The clinical course of these patients is one of progressive emaciation secondary anemia and excruciating pains in the affected bones.

The changes shown in roentgenograms of the bones invaded by tumor are usually osteoplastic. There is marked increase in density of the bone with areas of lighter mottling which suggest some destruction (Fig 358)

Simpson has reported a case in which there was no clinical, roentgenographic or gross anatomic evidence of vertebral metastases, which on subsequent microscopic

Simpson, W M Diffuse vertebral metastasis of prostatic carcinoma without bony changes, Am. J Roentgenol. 15 534 1926.

TABLE 65. MALIGNANT DISEASE OF THE MALE GENITAL TRACT WITH METASTASES TO BONE

A. CARCINOMA OF THE PROSTATE

B. U. I. No.	Race	Sex	Age	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor †	Roentgenogram	Duration of Primary Tumor Before Metastases, mos.	Interval Between Primary Treatment and Metastases, mos.	Result
19877	W	M	57	Right ischium		Irradiated, radium, March, 1930	Suggestive of metastases	21	26	
19566	W	M	78	Pelvis and spine	Pain	P.P. 31 y 1914	Positive for metastases	12		Dead 23 days after operation
19522	W	M	59	Spine		Irradiated	Suggestive of metastases	72		
19453	W	M	62	Right ischium		Irradiated radium, April, 1930	Positive for metastases	72	72	
19401	W	M	74	Spine and pelvis		Irradiated, radium, March, 1930	Positive for metastases	60		
19254	W	M	66	Sacrum	Pain	Irradiated	Positive for metastases	6		
19261	W	M	70	Pelvis	Pain	Irradiated	Positive for metastases	8	4	Dead
19239	W	M	70	Spine, pelvis		Irradiated	Positive for metastases	36	36	Dead 14 mo. later
19219	W	M	70	5th lumbar vertebra	Pain		Probable metastases	21–36	3	Dead less than 1 mo. after observation
19159	W	M	61	Pelvis		Irradiated, radium, J[illegible] 1930	Positive for metastases	12	12	
19102	W	M	61	4th lumbar vertebra and left ilium	Pain	Punch operation, Dec. 1921	Positive for metastases	36	36	
18789	W	M	64	Pelvis and lumbar vertebra	Pain		Positive for metastases	12		
18549	W	M	60	Ischium	Pain	Irradiated	Positive for metastases	12	12	
18522	W	M	60	Lumbar spine	Pain	Irradiated radium Aug. 1929	Positive for metastases	24	24	
18394	W	M	70	Pelvis, symphysis		Irradiated, radium July 1929	Positive for metastases	[illegible]		
18391	W	M	70	Left ilium	Pain 12 mo. after onset of urinary symptoms	Radium	Suggestive of metastases	18		
18139	C	M	65	Sacrum, left ischium, right ilium		P.P. Jan. 1929	Positive for metastases?	4		
18110	W	M	65	Right ischium, left ilium		Conservative P.P. Jan. 1929	Positive for metastases	24		
18045	W	M		Spine pelvis		Irradiated, radium, D[illegible] 1928	Positive for metastases	22		
18017	W	M	59	Sacro-iliac region	Pain	Radium, irradiated, 1928	Positive for metastases	4		Alive 6 mo. after treatment
18014	W	M	60	Lumbar vertebrae, symphysis pubis	Pain	Radium, Nov. 1928; irradiated	Suggestive of metastases	36–48	1	
17063	W	M	63	Vertebra, occiput, ribs (autopsy)	Headaches	Cystotomy Nov. 1929	No roentgenogram; metastases found at autopsy	3		Dead following operation
17874	W	M	60	3d lumbar vertebra		Radium, colostomy 1930	Positive for metastases	6		
17841	W	M	64	Pelvis	Pain	P.P. Jan. 1930	Positive for metastases	12		
17836	W	M	60	Left ilium		P.P. Oct. 1928	Suggestive of metastases	2		
17819	W	M	47	Seminal vesicle	Pain	Radium, April, 1927; irradiated	Positive for metastases	18		
17473	W	M	74	Left ilium	Pain	P.P. June 1928	Suggestive of metastases	24		
17461	W	M	66	Spine pelvis		Irradiated conservatively	Positive for metastases	24–36	24–36	
17277	W	M	52	Pelvis, sacrum	Pain	Irradiated	Positive for metastases	4		
17291	W	M	66	Spine pelvis		Irradiated radium, June 1928	Positive for metastases	27	27	

17391	W	M	67	4th lumbar vertebra	Pain	Irradiated (no data given)	Suggestive of metastases	12	14	
17307	W	M	70	Spine 4th and 5th lumbar vertebrae		Irradiated, conservative P.P. April 1, 1928	Positive for metastases	3	4	
17195	W	M	65	Right ilium		Radium, March, 1928	Suggestive of metastases	9		
17178	W	M	60	Spine pelvis		S.P., 1909 irradiated	Positive for metastases			
17164	W	M	84	Pelvis		Radium, 1925	Positive for metastases	36		
16922	W	M	72	Pelvis, skull	Pain	P.P. Jan., 1928	Positive for metastases	13		
16602	W	M	62	Pelvis, spine	Pain	Radium, Dec. 1927; irradiated	Positive for metastases	7		
16763	W	M	62	Lumbar vertebrae and pelvis		Punch operation, Nov. 1927	Positive for metastases	1		
16499	W	M	80	Lumbar vertebrae and pelvis		P.P. Sept. 1927	Positive for metastases	10		
16431	W	M	67	1st, 2d and 5th lumbar vertebrae		P.P. conservative Aug. 1927	Positive for metastases	13	15	Dead 16 mos. after operation
16419	W	M	60	2d lumbar vertebra	Pain	P.P. conservative Aug. 1927; irradiated Oct., 1927	Positive for metastases	6		
16379	W	M	67	Symphysis pubis		Excision of tumor March, 1927; postoperative radium and conservative P.P. July 1927	Positive for metastases	9	14	Alive and well over 2 yr. after second operation
16091	W	M	33	Lumbar vertebrae	Pain	P.P. conservative June 1927; irradiated	Positive for metastases	12		
16027	W	M	35	Right ilium, ischium, 5th lumbar vertebra	Pain	P.P., Aug., 1927; roentgen ray and radium, 3 years before	Positive for metastases	24		
15822	W	M	63	Lumbar vertebra and ribs		Irradiated, radium, May 1926	Positive for metastases	12	10	
15794	W	M	71	5th lumbar vertebra, sacrum, right ilium		P.P. April, 1927 radium	Suggestive of metastases	60		
15791	W	M	70	Lumbar vertebrae sacrum	Pain	Irradiated radium, March, 1927	Suggestive of metastases	18	6	Dead 1 mo. after treatment
15781	W	M	56	Pelvis, sacrum, coccyx	Pain	P.P. March, 1927	Strongly suggestive of metastases	24	12	
15647	W	M	61	Ilium, ischium, pubis	Sciatic pain	P.P. March, 1927	Positive for metastases	60–66		
15599	W	M	72	Pelvis	Pain	Radium, irradiated, 1926	Positive for metastases	36		
15504	W	M	66	Ischium, sacrum, lumbar spine	Pain	Irradiated, Feb., 1927	Positive for metastases	7		
15476	W	M	62	Spine, pelvis	Pain	P.P. Dec. 1926; irradiated	Positive for metastases	4		
15470	W	M	75	Symphysis pubis		P.P., conservative, Oct. 1926	Positive for metastases	6		
15371	W	M	60	4th lumbar vertebra, sacrum, ilium			Suggestive of metastases	48		Dead
15377	W	M	63	Pelvis		P.P. May 1926	Positive for metastases	4		
15316	W	M		Pelvis	Pain	P.P. conservative, Nov. 1926	Suggestive of metastases	28		
15275	W	M		Pelvis		P.P. Sept., 1926	Positive for metastases	12		
15241	W	M		Spine pelvis		P.P. Oct. 1926	Positive for metastases	18		Dead 1 mo. after operation
15154	W	M	66	Spine pelvis, right and left ischia		Radium advised	Positive for metastases	1		
14814	W	M	71	Sacrum, 5th lumbar vertebra	Pain	P.P., April, 1926	Suggestive of metastases	9		
14094	W	M	64	Sacro-iliac region		Radium, April, 1926,	Probable metastases	19	24	
14491	W	M	46	Right ilium		P.P. conservative, April, 1926	Suggestive of metastases	22	14	
14413	W	M	61	Pelvis		Radium, irradiated Feb., 1926	Positive for metastases	24		
14423	W	M	60	Sacrum, ilium, right ischium		Irradiated Dec. 1925	Positive for metastases	18		

† In this column P.P. indicates perineal prostatectomy; S.P. suprapubic prostatectomy

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TABLE 65 MALIGNANT DISEASE OF THE MALE GENITAL TRACT WITH METASTASES TO BONE (*Continued*)

R U L No.	Race	Sex	Age	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Roentgenogram	Duration of Primary Tumor Before Metastases, mos.	Interval Between Primary Treatment and Metastases, mos.	Result
14182	W	M		Sacrum, ilia			Positive for metastases	36		
14140	W	M	65	Left ilium, symphysis pubis, sacrum	Pain	P.P. 1922	Very suggestive of metastases	25	18	
13936	W	M	74	Ischium, right pubis, 2d lumbar vertebra	Pain	Radium, irradiated, Sept., 1925	Positive for metastases	13		
13913	W	M	73	Sacrum, ilium, pubes		Radium	Positive for metastases	6		
13767	W	M	69	Sacrum, ilium, lower lumbar vertebra	Pain	Irradiated Sept., 1921; radium July 1923	Positive for metastases	24		
13685	W	M	77	Ilia		Radium, July, 1923	Positive for metastases	48		
13471	W	M	66	5th lumbar vertebra, sacrum, ilium, left pubis	Pain	Cystotomy Nov 1921	Very suggestive of metastases	12		
13464	W	M	73	Pelvis	Pain		Positive for metastases	[illegible]		
13394	W	M	42	Right ischium	Pain	Radium, April, 1925	Positive for metastases	18		Dead few mos. later
13356		M		Pelvis, upper end of right femur			Positive for metastases			
13317	W	M	78	Pelvis, sacrum			Positive for metastases	31		Dead before treatment was begun
13311	W	M	77	Pelvis		P.P. March, 1925	Suggestive of metastases	[illegible]		Dead from operation
[illegible]	W	M	57	Pelvis	Pain		Positive for metastases			
12702	W	M	78	Right ilium		Radium, Sept., 1924	Probable metastases	3	1	
12595	W	M	74	Pelvis, lumbar vertebra	Pain	Irradiated, radium, Oct., 1924	Positive for metastases	0		
12550	W	M	65	5th lumbar vertebra	Pain	Irradiated, radium, March, 1924; P.P. Jan 1925	Beginning metastases			
12533	W	M	61	Right ilium		Irradiated	Positive for metastases	6		
12344	W	M	66	Ischium, right pubis	Pathologic fracture	P.P. June, 1924; postoperative irradiated	Positive for metastases	12		
12195	W	M	64	Spine, pelvis, sacrum	Pain	Radium, June, 1924	Positive for metastases	10		
L.198	W	M	67	Pelvis, lower lumbar vertebrae	Pain	Roentgen rays, radium, Jan. 1924; P.P., July 1924	Positive for metastases	24–36		
12499	W	M	63	Spine pelvis	Pain	Roentgen rays, radium, advised	Positive for metastases	6		
12278	W	M	70	Pelvis		P.P. May 1924	Positive for metastases	60		
12237	W	M	56	Spine pelvis	Sciatica of hip	S.P. May 1923; x-rays and radium	Positive for metastases	48		
12064	W	M	60	Symphysis pubis, left femur, right ilium		Punch operation and radium, Feb 1921; conservative P.P. March, 1921	Suggestive of metastases	12	2	Dead 18 mos. after operation
12080	W	M	63	Lumbar vertebrae, sacrum, ribs	Pain	P.P., radium, Feb., 1921	Positive for metastases	9		
12033	W	M	56		Pain	Irradiated, 1923	Sclerosis of vertebrae and bones of pelvis; no definite metastases			
11901	W	M	56	Sacrum, ilia	Pain	Irradiated, Nov 1922	Positive for metastases	5		
11942	W	M	66	3d lumbar vertebra, sacrum, ilia	Pain	Radium, irradiated, 1921 1922	Positive for metastases	24		
11625	W	M	66	5th lumbar vertebra, right ilium, pubis, sacrum	Pain		Positive for metastases	6		

11778	W	M	63	Pelvis, pubes, 4th and 5th lumbar vertebrae	Paraplegia	S.P. 1923	Positive for metastases	6		Dead (?)
11850	W	M	68	Sacro-iliac region, right		Irradiated, Aug. 1924	Positive for metastases	12		Dead 3 weeks after treatment
11878	W	M	63	Pelvis, sacrum	Pain	Radium, July 1923	Suggestive of metastases			
11532	W	M	74	Sacrum, pelvis		Radium, July 1923	Positive for metastases	30		
11467	W	M	67	Sacrum, spine	Pain	Radium, June 1923	Positive for metastases	36–48	2	
11419	W	M	57	Pelvis, lower lumbar vertebrae	Pain	Radium, June, 1923	Positive for metastases	60		
11335	W	M	67	Spine, pelvis, sacrum	Pain	Radium, April, 1923, irradiated, May, 1923	Positive for metastases	12		
11244	W	M	45	Spine, pelvis	Pain	P.P. irradiated, March, 1922	Suggestive of metastases	4	1	Dead 3 mos. after appearance of metastases
10409	W	M	73	Ribs, vertebrae	Pain	Punch operation after radium and irradiated, Dec., 1924	Roentgenograms negative; autopsy findings extensive metastases	24		
10919	W	M	75	Sacrum		Radium, Nov. 1922	Positive for metastases	24		Living 2½ yr. later
10778	W	M	64	Right ilium	Pain	P.P. conservative; radium, Sept. 1922	Positive for metastases	12	9	
10652	W	M	59	Spine, pelvis, sacrum	Pain	Radium, July 1922, irradiated	Positive for metastases	1½		Dead 4 mos. after x-ray treatment
10592	W	M	73	Femora, pelvis, spine, humerus, clavicles, scapulae	Pain	S.P. irradiated; radium, 1922 (June-July)	Positive for metastases	36		Dead
10517	W	M	78	Pelvis		Radium, June, 1922	Suggestive of metastases	3		
10445	W	M	76	Symphysis pubis, right hip	Pain	P.P. March, 1922; radium, March, 1922	Positive for metastases	12		
10191	F	M	67	Sacrum, ilia, 11th dorsal vertebra		P.P. radium, May 1922	Positive for metastases	12		Dead 7 mos. after operation
10478	W	M	71	Sacrum, pelvis		P.P. May 1922; radium, May 1922	Positive for metastases	18		Dead 11 mos. after operation
10400	W	M	73	Lower lumbar vertebrae		P.P. Feb., 1922, radium 3 weeks later (S.P. 10 months before)	Positive for metastases			
10091	W	M	76	Spine		P.P. April, 1923	Suggestive of metastases	1		
11055	W	M	57	4th and 5th lumbar vertebrae	Pain	Radium, Nov. 1921	Positive for metastases	13		
9855	W	M	75	4th and 5th lumbar vertebrae, pelvis	Pain	Radium	Positive for metastases	2½		
9493	W	M	64	Left ilium, sacrum	Pain	P.P., March, 1921	Positive for metastases	60	33	
9307	W	M	53	Sacrum		Radium and irradiated	Suggestive of metastases	36		
9018	W	M	65	Spine, pelvis	Pain	P.P. Oct., 1920		40	4	
8493	W	M	62	Pelvis	Pain	Radium, Feb., March, 1920	Positive for metastases			Dead 6 mos. after institution of treatment
8373	W	M	70	Spine, hips	Pain	P.P., Dec. 1919; radium, Jan., 1920; irradiated	Positive for metastases	42	6	Dead 13 mos. after appearance of metastases
8234	W	M	62	Spine, pelvis		P.P. Dec. 1919	Positive for metastases	133	34	Dead 2½ yr. after appearance of metastases
7272	W	M	69		Pain	P.P. Nov. 1918	Negative for metastases			Dead 1 yr. after operation
7240	W	M	61	Sacrum, coccyx	Pain	P.P. 1918	Positive for metastases	36		Dead 1½ yr. after operation
6959	W	M	59	Sacrum	Pain		Strongly suggestive of metastases			
6748	W	M	71	4th and 5th lumbar vertebrae, sacrum, ilia	Pain, 3 yr. incontinence of urine and feces	P.P. 1918 radium	Positive for metastases			

TABLE 65 MALIGNANT DISEASE OF THE MALE GENITAL TRACT WITH METASTASIS TO BONE (*Continued*)

B U I* N	Race	Sex	Age	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Roentgenogram	Duration of Primary Tumor Before Metastases, mos	Interval Between Primary Treatment and Metastases, mos	Result
6101	W	M	79	Lumbar vertebrae			Suggestive of metastases			
4417	W	M	65	Lumbar vertebrae, and pelvis		S P 1915 radium and irradiated	Positive for metastases	144	108	Dead 8 yr after operation
8131	W	M	57	5th lumbar vertebra, sacrum, ilium	Pain	P P 1909; punch operation, 1921; excision, 1927	Positive for metastases	120		

Cases from the Files of the Surgical Pathological Laboratory

N	Race	Sex	Age	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Roentgenogram	Duration of Primary Tumor Before Metastases, mos	Interval Between Primary Treatment and Metastases, mos	Result
42182	W	M	55	Pelvis		S P, May 1929	Positive for metastases			
33807	W	M	68	Pelvis		Irradiated 1922	Positive for metastases	21		
18375	W	M	57	Lower end of femur	Pathologic fracture	Amputation of leg, metastases, Oct., 1913	Positive for metastases	6		Dead few months after treatment
10341	W	M	54	Upper third of femur	Pain, pathologic fracture		Positive for metastases			Dead following operation
1813	W	M	78	Tibia, shaft	Swelling	Amputation of thigh (metastatic growth) Jan 1907		10	3	Dead few days after observation; Dead 8 mos. after operation

B Testicular Malignant Disease

Path. N	Race	Sex	Age	Primary Tumor	Location of Metastases	Symptoms Attending Appearance of Metastases	Treatment of Primary Tumor	Roentgenogram	Treatment of Metastases	Duration of Primary Tumor Before Metastases, M	Interval Between Primary Treatment and Metastases, Mo.	Result
42806	W	M	46	Sarcoma of testicle	Skull, frontal bone	Tumor	Excision of right testicle, April, 1930	Positive for metastases	Irradiated, April, 1930	8	Duration of metastatic growth 10 mo	Dead 3 mos. after operation
20601	W	M	40	Carcinoma of testicle	Ribs, 4th and 5th	Pain	Orchidectomy Feb 1922; postoperative radium	Positive for metastases	Radium, irradiated March, 1922	2	Metastases observed: roentgenogram 2 mos. before symptoms of primary tumor	Well 3 yr 9 mos. after operation

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Fig 338 (No 42182) Osteoplastic nature of bony metastases from carcinoma of the prostate as depicted in the roentgenogram. (*Top left*) Involvement of pelvis by osteoplastic metastasis. (*Top right*) the upper end of the humerus with marked sclerosing reaction in the region of the head. (*Center*) shows multiple involvement of the entire pelvis and associated involvement in the upper part of both femurs. Note again the marked production of bone in the affected areas.

study revealed generalized skeletal metastases from medullary carcinoma of the prostate gland.

Bumpus, in a study of 362 cases at the Mayo Clinic, found that the osteoplastic type of bone metastasis was by far the more common but that osteoclastic changes did occur in a few of the cases.

Bumpus, H C Jr Carcinoma of the prostate Surg Gynec. & Obst. 32 31 1921

In early cases of osseous involvement with doubtful findings in the prostate gland on palpation, the diagnosis of metastatic prostatic carcinoma is aided by determining the serum acid phosphatase In carcinoma of the prostate the acid phosphatase is elevated. This determination is also valuable following prostatectomy when recurrence of the disease is suspected with or without

only one instance is there a record of metastases (Table 65B)

A man, aged 40 (No. 29669) at the age of 18 after an attack of measles, developed orchitis of the left testicle with subsequent atrophy For two months prior to admission, the patient had noted swelling in the testicle. On examination, it was found to be a hard, irregular mass. There was no enlargement of the regional lymph glands and no palpable mass in the abdomen The blood and urine were normal. *On roentgen examination of the various bones, the fourth and fifth ribs showed destruction.* The patient had noted some pain in the region of these lesions for over a year Just prior to admission, there had been a noticeable loss of weight. Following roentgen therapy both over the testicle and the affected ribs, orchidectomy was performed, and uneventful recovery followed. In 1922, the patient had remained well 28 months with recalcification of the fourth and fifth ribs. Since that time the patient has been lost from observation.

In 42 cases of "teratoma of the testicle there is one instance of metastases to the bone (Table 65B No 42856)

A white man, aged 56 presented himself with a growth on his forehead of 11 months duration. When first noticed, it was the size of the index finger There had been no pain or headache. A swelling of the right testicle had been noticed for at least a year and a half which followed a slight injury Six months prior to his admission to the hospital, the swelling suddenly disappeared, with subsequent fluctuations in size Seven weeks before the patient had what he called an attack of influenza, with a temperature of 102 F Following this, a physician was seen who gave the patient serum treatment for the tumors, *which was followed again by an elevation of* temperature On examination the tumor in the forehead was found to be the size of a small orange and to extend from the nose to the hair line There was fluctuation in the tumor



Fig. 380. Roentgenogram of the pelvic bones showing invasion of the ileum and sacrum by extension of tumor from the uterus.

The roentgenogram revealed destruction of the frontal bone particularly of the outer table immediately above the frontal sinuses, with infiltration and swelling of the overlying soft structures. There was no evidence of metastases in the other bones of the skeleton. The testicle was removed and the patient was given roentgen therapy with rapid disappearance of the tumor in the forehead, which was soon followed, however by vomiting and other systemic disturbances. There was never severe anemia or emaciation. The patient died 3 months after operation, having lived 14 months from the first sign of the metastases.

We have been unable to find an extensive series of cases in the literature reporting testicular malignancy with skeletal metastases. Vosburgh and Alderman report a single case with metastases to the vertebrae and cite two other cases, one reported by Kennedy and Stevenson, and the other by Bricka and others. Sutherland and his coworkers record two cases.



Fig. 361. (No 29529) Roentgenogram depicting invasion of the lower end of the femur by ovarian tumor Note the destruction of the bone and the subperiosteal involvement on the posterior aspect.

Tumors of the Bladder

One example of carcinoma of the bladder with metastases to bone (Table 66 No 11970) is recorded.

A white woman, 50 years old, six weeks before admission to the hospital felt pain in the inner portion of the right tibia on walking. This was followed by swelling of the right foot. The pain was worse at night, and marked swelling developed in the midshaft of the tibia. On roentgen examination there was evidence of destruction of the bone beneath the periosteum on the side toward the fibula with slight evidence of formation of new bone, characteristic of metastatic cancer Resection of the tibia was performed and microscopic examination revealed cells of the transitional type resembling that seen in tumors of the bladder

Following the operation, hematuria developed, and after two months and nine days a cystoscopic examination was done which showed a tumor of the bladder in the region of the trigone. Unfortunately the patient was lost from observation soon after recovery from operation so that the ultimate result could not be ascertained.

Tumors of the Uterus

From among 88 cases of carcinoma of the uterus or cervix, 5 (5.6 per cent) showed

metastases to bone (Table 66) 2 of these patients having the primary lesion in the cervix. The age incidence in these cases extended from 35 to 60 years. The metastases were found four times in the pelvis, twice in the femur and once in the humerus, skull and metacarpals of the right foot.

This is not the case in cervical carcinoma, which invades the parametrium early The duration and type of the disease undoubtedly influence the rapidity of the extension. The clinical course of the advancing disease is dominated by secondary invasion of surrounding organs, many cases terminating through uremia from occlusion of the ureters. Characteristic cachexia develops in most cases, but nutrition may remain surprisingly good.



FIG. 362. (No 26823) Metastatic thyroid carcinoma. Microscopic picture showing marked proliferation of tumor cells, with a spicule of old bone being destroyed by direct contact with the tumor cells.

Varying degrees of pain with disturbances of function in the affected extremities were common symptoms. At times, an associated swelling was noted in the regional glands.

Owing to the fact that uterine carcinoma invades lymph nodes relatively late, there is a striking tendency for the disease to remain localized either to the uterus or to its immediate vicinity As a rule tumors of the fundus long remain confined by the muscular wall.

The roentgenogram shows destruction of the bone (Fig 360) There is little tendency to ossification, and there is nothing typical of the lesion to set it apart from the other osteoclastic types of metastases.

In this group of cases there is little to offer with regard to treatment except the

general principles that have been laid down in the preceding pages. Ford[*] recently showed that there is a slightly smaller percentage of cases showing distant metastases in carcinoma of the cervix, following adequate irradiation of the primary lesion, than in those cases in which radium therapy is not employed. Some relief from pain in the osseous lesions is obtained by irradiation, but this is more transient than the relief following the irradiation of mammary carcinomatous metastases to bone.

Tumors of the Ovary

There are two instances, 2.8 per cent, of ovarian tumor with metastases to bone among 69 such cases studied (Table 66).

One of these patients was a woman, aged 47 (No 27170) in whom four months prior to admission, sudden pain developed over the entire abdomen, and lasted for a few days. The abdomen soon became filled with fluid, a subsequent laparotomy was performed, and bloody fluid was found. The right ovary was much enlarged. The patient made an uneventful recovery and returned home Twelve months later she began to limp because of discomfort in the right foot. A roentgenogram of the foot showed destruction at the proximal end of the third metatarsal bone. Roentgen therapy was administered, and the condition of the foot improved. The patient has been lost from observation.

The other case (No. 29529) was that of a young girl, aged 14, who first noticed pain in the left knee with limp and pains in the abdomen with some diarrhea Eight months later a lump appeared on the posterior portion of the skull A laparotomy was subsequently done for pain in the abdomen free fluid was found, and a small tumor of the right ovary was removed and was diagnosed sarcoma (mesothelioma)

Table 67 Cancer of the Thyroid with Metastases to Bone

Pathologic No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
40840	W	F	51	Carcinoma of thyroid	Upper end of left humerus		Exploration	
40972		M	66	Sarcoma of thyroid	Bone		Irradiated	Lived 16 mos.
37300	W	F	58	Carcinoma of thyroid	Skull			
31358	W	M	70	Carcinoma of thyroid	Ribs and sternum, right 6th 7th and 8th ribs			Lived 24 mos
28966	W	M	48	Carcinoma of thyroid	Neck of femur	Femur	Curetting of tumor	
26752	W	F	34	Carcinoma of thyroid	Upper third of right humerus, right clavicle	Right clavicle	Erysipelas and prodigiosus toxins (Coley) radium, amputation and irradiated	Lived 21 mos.

Roentgen therapy was instituted, and though some relief from pain followed, the course was progressively downward. The patient died 20 months after the first symptoms of metastases. Roentgen examination revealed areas of destruction in the skull and in the lower third and the upper end of the femur (Fig 361) and in the left ilium

MALIGNANT DISEASE OF THE THYROID

In those reports that deal with a large series of cases of malignant disease of the thyroid, metastasis to bone is of frequent occurrence. Ehrhardt* found bones affected in 66 of 238 cases of carcinoma of the thyroid, and Ewing† is of the opinion that in malignant conditions of the thyroid the bones are involved only less frequently than in cases of mammary and prostatic cancer giving the following order of frequency in bones affected skull, sternum, spine, ribs, humerus, femur and pelvis. The metastatic growths appear near the epiphy

[*] Ford, F A.: Distant metastases in carcinoma of the cervix of the uterus, Minnesota, Med. 13 489 1930.

* Ehrhardt, O : Bruns Beiträge z. kl. Chirurgie 35 813 190..

† Ewing, J Neoplastic Diseases, ed. 3, Philadelphia, Saunders, 1928 p. 955

ses either as central (Fig 363) or subperiosteal lesions. Much has been written concerning the so-called metastatic tendencies of the "benign metastasizing goiters." Simpson reported three cases in which the microscopic picture of the tissue removed from bone was that of typical thyroid tissue in patients with apparently benign goiters, but on careful observation of the clinical course and subsequent pathologic changes, these cases were found to show malignant change in the thyroid gland. This, together with evidence which he accumulated, points to the fact that many such tumors in the thyroid gland have some malignant change.



Fig 363A. (No. 26823) Roentgenogram depicting involvement of the bone in the upper end of a humerus by carcinoma from thyroid. Note the marked destruction and expansion in the region of the nutrient vessels. There is also evidence of diffuse involvement of the lower portion of the shaft without distortion.



Fig. 363B Metastatic carcinoma from the thyroid involving the shaft of the humerus.

In the six cases of malignant disease in the thyroid gland, with metastases to bone (Table 67) the ages ranged beyond 40 well into late life. The sexes were equally divided.

The series is too small to draw any conclusions as to the incidence of bone involvement, but the evidence points to both a lymphatic and a hematogenous type of invasion.

The clinical course was usually marked by progressive emaciation, with symptoms referable to the bones that were the seat of the metastases. Pulmonary symptoms when the tumor had invaded the structures of the

Simpson, W M. Three cases of thyroid metastasis to bones, Surg Gynec & Obst 42 489 1926.

neck and the mediastinum and caused pressure were marked in some cases.

Roentgen therapy, erysipelas and prodigiosus toxins (Coley) and radium therapy with subsequent amputation were variously combined, but despite the alleviation of pain, the disease usually proved fatal within two years.

The microscopic picture shows marked proliferation of tumor cells with little or no attempt at bone repair. Spicules of old bone are destroyed by direct contact with the tumor cells (Fig. 362).

In Sutherland, Decker and Cilley's series of cases, metastatic malignant lesions in bone arising from primary tumors of the thyroid gland were seen in 19 cases. All but one occurred in patients who were in the fifth, sixth or seventh decade of life. One patient was in the fourth decade. In the skull, the lesions presented interesting types of osteoclasis. In one case there was wide destruction of the cranial vault, with apparent extension of the periosteum out over a shadow of soft tissue, not unlike that seen in a case in which spontaneous decompression has been followed by cerebral hernia. In a second case there was a punctate type of destruction and the patient had associated nodules in the scalp. In the third case there was a localized area of osteoclasis in the parietal area. The lesions of the spinal column were all of the osteoclastic variety, and those in the pelvis gave evidence of extensive destruction of bone without evidence of proliferation. The femurs and shoulder girdle were included in a general involvement. The ribs in one case were a part of a general involvement, in the other there was localized destruction of the sixth rib with expansion of the cortex, and a surrounding area of involved pleura.

MALIGNANT DISEASE OF THE GASTRO-INTESTINAL TRACT

Stomach

The literature on carcinoma of the stomach with metastases to bone is limited. Moore,* of the Mayo Clinic, up to 1919 had not observed a single metastatic lesion to bone from cancer of the stomach. Kaufmann† reported 2.5 per cent of metastases to bone in a review of 309 cases of malignant disease of the stomach. Schlesinger† found an incidence of 9.3 per cent in 54 cases, and Jenkinson,‡ in reviewing the literature, could find only 32 cases in which carcinoma of the stomach had metastasized to bone.

From our series of 537 patients with carcinoma of the stomach, only 7 or 1.03 per

Table 68. Carcinoma of the Stomach with Metastases to Bone

Path. N.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
41[illegible]	W	F	84	Carcinoma of stomach	Sternum, vertebra, femur, ribs, pelvis			
42246	[illegible]	M	33	Carcinoma of stomach	Bones			
42244	W	F	70	Carcinoma of stomach	8th left rib			
42342	W	M	39	Carcinoma of stomach	Right 4th, 8th and 9th ribs, left 4th, 8th and 9th ribs, 1st lumbar vertebra, 1st and 10th thoracic vertebrae, left parietal bone			
42340	W	M	40	Carcinoma of stomach	Right femur and ilium, 2d and 5th right ribs		Rest in bed	Lived 9 mos.
30012	W	M	[illegible]	Carcinoma of stomach	Lower third of right femur, left ilium, right acetabulum	Femur		Lived 24 mos. plus
36342	W	M	71	Carcinoma of stomach	Left scapula		Irradiated	Lived 14 mos.

* Moore, A. B.: A roentgenological study of metastatic malignancy of the bones, Am. J. Roentgenol., 6: 589, 1919.

† Quoted by Jenkinson.

‡ Jenkinson, E. L.: Primary carcinoma of the gastro-intestinal tract accompanied by bone metastasis, Am. J. Roentgenol., 11: 411, 1924.

cent, were found to be affected by metastases to bone (Table 68) The ages of these patients ranged between 32 and 71 The bones involved were, in the order of frequency ribs, 4 cases pelvis and femur 3 cases vertebrae, 2 cases sternum, skull and scapula 1 each.

the ribs resembled more a shriveling of the bone than definite destruction. Lesions in the pelvis were characterized by localized areas of destruction

The frequent involvement of the ribs without metastases to the lungs points to a lymphatic route of dissemination, while



FIG. 364. (No. 36342) Roentgenogram showing diffuse mottling with destruction of the bone in the head of the humerus and in the adjoining scapula from metastasizing carcinoma of the stomach.

In a series of cases reported by Sutherland and others, metastatic lesions to bone from primary gastro-intestinal malignancies were seen in 1.9 per cent of the cases. In practically all the cases, an osteoplastic type of reaction was observed in the roentgenogram. Multiple masses of denser tissue were seen throughout all the bones affected, and there was an accentuation of the trabecular elements. Lesions were located in the ilium and the ischium, the upper humerus, the cervical, thoracic and lumbar vertebrae, and the ribs. Lesions in

the mode of invasion to more distant bones is open to question.

In one instance (Path No. 39012) a pathologic fracture was found at the lower third of the right femur

Most of the metastatic lesions in this group were examined at autopsy but in two instances in which roentgen examinations were recorded (Figs. 364 and 365) either diffuse mottling with destruction of bone and no distortion of the bone shell was present, or a slight expansion accompanied the central rarefied lesion.

The clinical course is well illustrated in the following case report (No. 43240)

A white man, aged 40 was admitted to the hospital complaining of an inability to walk, with pain in the legs and in the back of the neck. He had previously suffered for nine months with a sensation of pins and needles in the feet on walking His feet felt cold, and the skin was exceedingly dry over these extremities. Seven months prior to admission, he had fallen on his back, and severe pain had followed for several days Four months later a progressive weakness of the legs was noted and finally an inability to walk. Occasionally he had suffered from attacks of vomiting, and there was constant headache.

On examination, the patient was found to be quite emaciated, and he was unable to sit up in bed, the knee jerks and deep reflexes were absent. There was a fulness over the outside of the crest of the right ilium and a distinct thickening of the head of the femur The blood showed a moderate secondary anemia, which gradually became more severe. The clinical course was progressively downward, and the patient died nine months after the first symptoms of metastases.

An interesting feature of the blood in cases of metastases of the bone from carcinoma of the stomach is reported by Piney and others.* Changes in the blood like those in pernicious anemia were found in these cases, and are recorded in only one other type of metastatic tumor—carcinoma of the breast metastasizing to bone. This is in contrast to the ordinary type of secondary anemia usually seen. In one case (No. 44477) a similar condition was noted in the blood.

A white woman, aged 54 had always been healthy until three years before admission to the hospital, when she became quite weak and pale and began losing weight.

Six months before admission to the hospital she noticed enlargement of all the lymph nodes and progressive weakness with fever and sweats. The blood on admission revealed 3 100 000 red blood cells, 10 000 white blood cells, 340 000 platelets with 30 per cent of polymorphonuclear cells, 6 per cent eosinophils, 2 per cent basophils, 26 per cent myelocytes, 1 per cent myeloblasts, 16 per cent large lymphocytes and 11 per cent small lymphocytes, and also tertian malarial parasites which were present at this examination.



FIG. 365 (No. 39012) Roentgenogram showing diffuse cystic destruction in the lower shaft of a femur from carcinoma of the stomach metastasizing to the bone. In the shaft above the area of destruction the cortex is seen to be eroded from within.

A roentgenogram of the chest showed enlarged mediastinal glands, and at this time the long bones were normal. Chemical examination of the blood showed nothing unusual, and a Wassermann reaction was negative.

A lymph gland was removed for diagnosis, and the microscopic picture (Fig 366) was thought to be myeloid leukemia.

The further course of the disease was one

* Parmentier E., and Chabrol, E. Anémie grave et métastases cancéreuses dans la moelle des os, Bull. et mém. Soc. méd. d. hôp. de Paris 26 341 1909 Schleip, K. Zur Diagnose von Knochenmarkstumoren aus dem Blutbefunde, Ztschr f klin. Med. 59 261 1906. Harrington, A. W and Kennedy A. M.: Bone marrow metastases and anemia in gastric carcinoma. Lancet 1 376, 1913.

of progressive emaciation. The anemia became very marked, and fifteen days after admission to the hospital the patient died.

Autopsy was performed, and a large tumor of the stomach with extension to surrounding tissue and mesentery was found. The retroperitoneal, mediastinal, peribronchial, cervical, axillary and inguinal lymph nodes the spleen, liver and bone (Table 68) were involved.

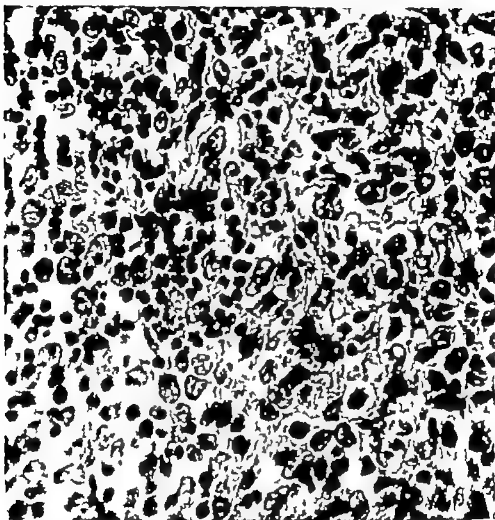


Fig 366. (No 44477) Photomicrograph showing invasion of a lymph node by tumor tissue from medullary carcinoma of the stomach.

The microscopic picture of the tumor of the stomach (Fig 367) revealed medullary carcinoma.

The bone marrow was diffusely destroyed, and it was easy to distinguish between bone marrow and tumor tissue.

LEUKEMOID REACTION

Leukemoid reactions with metastatic carcinoma of bone occur in about 3 per cent of cases with osseous metastasis. We have found this reaction more often with gastro-intestinal carcinoma, but it has been reported with metastasis to bone from cancer of the breast and prostate (Heck and Hall) and in bronchogenic carcinoma (Lin and others) The metastases are usually accompanied by myelofibrosis. The hemopoiesis may be stimulated by the starvation of the hemopoietic cells, through the metabolic demands of actively growing cancer plus the fibrosis. It is not necessarily due to extramedullary hematopoiesis, nor is it due to simple bone-marrow displacement, since it is relatively rare with any form of skeletal metastasis.

The leukemoid reaction may be of the myelocytic or lymphoid type. A list of vari-

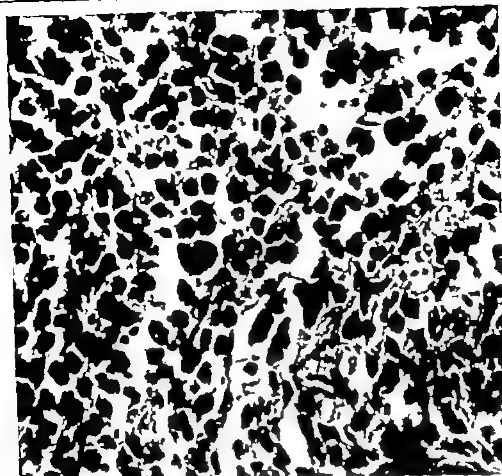


FIG. 367 (No 44477) Photomicrograph showing primary medullary carcinoma of the stomach which subsequently metastasized to bone

ous cases for both types of leukemoid reaction is shown in the accompanying table.

TABLE 60 LEUKEMOID REACTIONS

Myeloid Type	Lymphoid Type
Pyogenic infection	Infectious mononucleosis
Nonpyogenic infection	Measles
Miliary tuberculosis	Pertussis
Hemolytic anemia	Typhoid fever
Pernicious anemia	Puerperal sepsis
Massive hemorrhage	Metastatic carcinoma to bone
Hodgkin s disease	
Metastatic carcinoma to bone	
Multiple myeloma	
Diabetic coma	
Mustard gas poisoning	

The leukemoid reaction is usually accompanied by an elevation of the total white-cell count from 20-30 000 Cell counts as high as 50-100 000 have been observed. When the myeloid reaction occurs, 2-5 per cent of the leucocytes are of the immature form. The same is true of the lymphoid type of reaction. In such cases, erythroblasts are present in the blood smear and a relatively severe anemia also characterizes the blood count. The platelet count may be lowered to 100 000 or less and symptomatic purpura may be present. The tourniquet test is usually positive and the bleeding time may be prolonged from 8 to 10 minutes.

Tumors of other parts of the gastro-intestinal tract occasionally metastasize to the skeletal system, and are recorded in the literature as isolated case reports.

* Moon, V H.: Primary carcinoma of the liver with metastases to bone, Arch. Path. 8 938, 1919 Brickner W M., and Milch, H Pathological fracture of the humerus from carcinomatous metastases, oesophageal, Internat. Clin. 1 207 1926.

Among the primary lesions in this laboratory single examples of invasion of the bone from malignant conditions of the esophagus, cecum, sigmoid, rectum, ileum and liver are recorded (Table 70)

Only one patient in the series was treated by roentgen therapy with some relief from pain but apparently without prolongation of life.

TABLE 70 MALIGNANT DISEASE OF THE GASTRO-INTESTINAL TRACT WITH METASTASIS TO BONE

Path N	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
Carcinoma of the Gastro-Intestinal Tract								
29661				Carcinoma of esophagus	Lumbar spine			
29661½				Carcinoma of cecum	Ischii and pubis			
29661¾				Carcinoma of sigmoid	Upper third of right femur			
3145	W	F	34	Carcinoma of rectum	Midshaft of right humerus	Humerus		Living after 18 mos. lost from observation
Sarcoma of Gastro-Intestinal Tract								
28238½	W	F	18 mo.	Sarcoma of ileum	Right ilium, left femur Right femur left ilium		Radium	Dead
Primary Carcinoma of the Liver								
25501	[illegible]	M	70	Carcinoma	Pelvis, upper end of femur spine			Lived 6 mos.

CARCINOMA OF THE LUNG

Involvement of the bone was found in four (16 per cent) of 24 cases of carcinoma of the lung analyzed in this laboratory Grove and Kramer * in a study of 21 cases of primary lesions of the lung, found 38 per cent metastasizing to bone. A wide variety of bones were involved, including the lumbar spine, pelvis, ribs and skull (Table 71) Pathologic fracture was found in the ribs of one case at examination.

Adler reported 327 cases of pulmonary carcinoma with generalized metastases in 294 cases. In this group 47 cases, or 14 per cent, had osseous metastases. The osseous tumors may involve the region below the knee or the elbow Hirsch and Ryerson reported a lesion in the radius and another in the tibia. Matthews reported a lesion in the carpal bone. Sutherland, Decker and Cilley studied 18 cases of bronchogenic carcinoma with osseous involvement. In every case the metastases involved the vertebral column. Osteoclastic lesions, rather than osteoplastic, characterized the roentgenogram.

The clinical course of the disease reveals nothing different from that recorded in other metastatic lesions. The roentgenogram shows destruction of the bone with slight formation of new bone, often within the area of destruction (Fig 368) Microscopically the osseous lesion shows destruction of the bone by direct contact with the tumor cells and some attempt on the part of the bone to react by fibro-ostosis (Fig 369)

Hirsch and Ryerson* reported four cases

Grove, J S., and Kramer S E. Primary carcinoma of the lung, Am. J M. Sc. 171 250, 1926.

Hirsch, E. F., and Ryerson, E. W : Metastases of the bone in primary carcinoma of the lung: review of so-called endotheliomas of bone, Arch. Surg. 16 1, 1928.

in which the early diagnosis was that of "endotheliomas" of bone and they urged complete autopsies in all so-called primary endotheliomas of the bone in order to rule out metastases from tumors of the lung The advice of these authors applies equally to other skeletal metastases. Metastatic thyroid tumors, hypernephromas involving bone and particularly nonpigmented melanomas with osseous metastases have been frequently reported as endotheliomas, angioendotheliomas, or hemangioendotheliomas of bone. We have rarely observed a verified malignant hemangioendothelioma of bone, (see Chap 21) and believe most of the cases reported are metastatic carcinoma to bone from an undetermined primary focus

TABLE 71 MISCELLANEOUS TUMORS WITH METASTASES TO BONE

Path N	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
				Carcinoma of the Lung				
40542	W	M		Carcinoma of lung	Lumbar spine pelvis, skull		Irradiated	
27838	W	M	30	Carcinoma of lung	Right 9th rib		Resection	Lived 21 mos.
31740	W	M	40	Carcinoma of lung	Ribs, vertebrae	3 ribs		
14800	N	F	84	Carcinoma of lung	Skull		Excision of frontal bone	
				Melanomas				
33176	W	M	44	Melanoma	Middle third of left humerus	Middle third of	Amputation of left arm	Living 7 yr., 6 mos.
10784	W	F	79	Melanoma	Upper third of tibia			Lived 36 mos.
9717	W	M	70	Melanoma	Ribs, clavicle radius			
				Nasopharyngeal Tumor				
40299	W	M	67	Adenoid cystic basal cell carcinoma	Skull, jaw cervical vertebrae, clavicles, scapulae, all ribs, other bones		Excision of nasal polyp	Lived approximately 36 mos.
				Epithelioma of Ear and Heel				
25035	W	F	40	Epithelioma	Lower end of femur		Cauterization of lower end of femur erysipelas and prodigiosus toxins (Coley's)	
20431	W	M		Epithelioma	Malar bone		Irradiated radium	Lived 30 yr plus
				Sarcoma of the Soft Parts				
20088	W	M	22	Sarcoma of neck	Clavicle, lower right jaw tibia		Roentgen rays, erysipelas and prodigiosus toxins (Coley's)	Lived 24 mos. plus
24482	W	M	32	Sarcoma of neck	Right clavicle, ilium, radius, left tibia, ankle		Irradiated	

OTHER PRIMARY TUMORS

MELANOMAS

Melanoma* developing in a benign pigmented mole is not unusual, but few examples are cited in which metastasis to bone occurs. In a study of 169 cases, only

* The term malignant melanoma is preferred by some who use the term benign melanoma for pigmented moles of benign character



FIG. 368. (No 14500) Metastatic carcinoma of lung Roentgenogram of the skull showing destruction of the bone with slight formation of new bone within the area of tumor invasion.

3, or 1.07 per cent, showed secondary deposits in bone (Table 71)

The location in the long bones is at the site of the nutrient vessels (Figs. 370 and 371) Destruction and expansion of the bone and some invasion of the soft parts may occur

Pathologic fracture occurred in one instance in the middle third of the humerus emphasizing the destructive character

Pain extending over a period of a year or more, occasionally pathologic fracture and ultimately the symptoms of generalized dissemination of cancer are outstanding features. However there is a patient living seven years and six months following amputation of the left arm for a metastatic lesion in the middle third of the humerus (No. 32176) which was proved to be a malignant pigmented mole by microscopic study

A white man, aged 44, had pain in the middle of the left humerus eight weeks prior to admission. Swelling began soon after and was accentuated by the use of the arm. The examination gave negative results, except for the left arm, where there was a cylindric swelling in the middle third with slight local redness of the skin. The pathologic fracture was found at this examination.

TABLE 72 METASTASIS IN BRONCHOGENIC CARCINOMA

To	Jaffe 100 Autopsied Cases	Ochsner and DeBakey 3047 Collected Autopsies	Perrone and Levinson 38 Autopsied Cases	Present Series 36 Autopsied Cases
Thoracic lymph nodes	89%	72 2%	20 8%	47 6%
Other lung	43	[illegible] 3	10 4	36 4
Adrenals	42	20 3	20 8	44 8
Abdominal lymph nodes	37		33 8	14 0
Liver	36	33 3	15 0	47 6
Kidneys	28	17 5	5 2	22 5
Bones	22	21 3	2 6	39 2
Brain	10	16 5		19 6
Intestines	8	4 8	13 0	8 4
Heart	7	12 7+	13 0	5 6
Pancreas	6	7 3	7 8	11 2
Spleen	5	3 5		5 6
Peritoneum	4	4 8	15 6	5 6
Skin	2	3 6	26 0	11 2
Pericardium	2		31 6	14 0
Pleura		29 [illegible]		22 4

From Henkin William A Ann Int Med 27: 235, 1947

The arm was amputated and the microscopic examination revealed cells with the morphology of malignant melanoma

Melanotic pigment was found incorporated in many of the cells. No further treatment was instituted, and in January 1930 the patient was reported well, seven years and six months after the onset of symptoms.

Other isolated examples of metastases from various primary tumors to bone are shown in Table 71.

An interesting nasopharyngeal tumor of the adenoid-cystic basal-cell carcinoma type is to be noted, which after several recurrences and much radium therapy with excision of the primary nasal polyp on many occasions has ultimately metastasized to the skeleton the patient having lived 36 months from the onset of the osseous invasion The bones involved were the skull, jaw cervical vertebrae clavicles, scapulae all of the ribs, pelvis and femurs (Fig. 372)

Table 73. Cases of Undetermined Primary Lesions with Metastases to Bone

Path No.	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
43229	W	M	43	Carcinoma	Upper third of left femur, left ilium	Left femur	Exploration	
42924		M	58	Undetermined	1st lumbar vertebra		Laminectomy	
41708	W	M	36	Undetermined	Left femur	Left femur below trochanter		Lived 10 mos.
40816	W	F	49	Undetermined	All ribs, dorsal spine, lumbar spine, cervical spine, sternum, scapula, clavicles, humeri, femora		Irradiated and lead	
40734		F		Undetermined	Skull, pelvis, thoracic vertebrae, femur, ribs	Ribs, femur		Lived 15 mos.
30914	W	M	60	Undetermined	Right humerus, left humerus, spine	Right humerus	Irradiated	
30576	W	M	31	Undetermined	Skull, upper third of right femur	Upper third of right femur	Irradiated	Lived 30 mos.
39706	W	F	66	Undetermined	Ilium, left acetabulum	Ilium	Irradiated	Lived 27 mos.
37538		M	21	Sarcoma	Right temporal bone			
37465	W	M	43	Undetermined	Shaft, humerus and right femur			Lived 43 mos.
37390	W	F	70	Undetermined	Upper third of left femur	Femur		
36179	N	F	58	Carcinoma	Middle third of right femur	Femur	Amputation of right leg	Lived 18 mos.
36118	W	M	49	Carcinoma	Shaft of femur	Femur	Curettement	Lived 24 mos.
35928				Undetermined	7th dorsal vertebra, rib, femur			
33618	W	F		Undetermined	Upper third of left femur, tibia, fibula, left pubic bone	Femur	Irradiated	Lived 21 mos.
33310	W	M		Undetermined	Humerus		Prophylactic toxin treatment, biopsy and amputation	Living 45 mos. 1928
33002	W	M	28	Undetermined	Pelvis, 4th lumbar vertebra			
34992	W	F	33	Carcinoma	Right clavicle		Irradiated	Lived 8 mos.
31200	W	M	67	Colloid carcinoma	Upper third of right humerus		Amputation of right arm	
34101	W	M		Carcinoma	Clavicle		Resection of tumor	

Spies* has collected a number of these cases. He found that the tumors are usually situated in the region of the nasopharynx, nasolabial fold, or about the buttocks, and that many of them metastasize after repeated recurrences.

Bone Involvement in Neuroblastoma of the Adrenal

In children under the age of five years a rare malignant tumor may arise from undifferentiated nervous tissue found in the

Smith, D T Method for making a differential diagnosis between xanthomatous and melanin tumors from frozen sections, Arch. Surg 8 903 1924

Spies, J W: Adenoid cystic carcinoma; generalized metastases in 3 cases of basal cell type, Arch. Surg. 21 365 1930.



FIG. 368. (No. 14500) Metastatic car cinoma of lung Roentgenogram of the skull showing destruction of the bone with slight formation of new bone within the area of tumor invasion

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To	Jaffe 100 Autopsied Cases	Oechsner and DeBakey 3047 Collected Autopsies	Perrone and Levinson 38 Autopsied Cases	Present Series 36 Autopsied Cases
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Other lung	43	23 3	10 4	26 4
Adrenals	42	20 3	20 8	44 8
Abdominal lymph nodes	37		33 8	14 0
Liver	30	33 3	15 0	47 6
Kidneys	28	17 5	5 2	23 6
Bones	22	21 3	2 6	39 2
Brain	19	16 5		19 6
Intestines	8	4 3	13 0	8 4
Heart	7	12 7+	13 0	5 6
Pancreas	6	7 3	7 8	11 2
Spleen	5	3 5		5 6
Peritoneum	4	4 8	15 6	5 6
Skin	2	3 6	26 0	11 2
Pericardium	2		31 8	14 0
Pleura		29 8		22 4

* From Henkin William A Ann Int. Med 27: 235 1947

The arm was amputated, and the microscopic examination revealed cells with the morphology of malignant melanoma.

Melanotic pigment was found incorporated in many of the cells. No further treatment was instituted, and in January 1930 the patient the skeleton, the patient having lived 36 months from the onset of the osseous invasion. The bones involved were the skull, jaw, cervical vertebrae, clavicles, scapulae, all of the ribs, pelvis and femurs (Fig 372)

TABLE 72. CASES OF UNDETERMINED PRIMARY LESIONS WITH METASTASES TO BONE

Path N	Color	Sex	Age	Primary Tumor	Location of Metastases	Pathologic Fracture	Treatment of Metastases	Duration of Metastases
45226	W	M	43	Carcinoma	Upper third of left femur, left ilium	Left femur	Exploration	
42924		M	38	Undetermined	1st lumbar vertebra		Laminectomy	
42706	W	M	36	Undetermined	Left femur	Left femur below trochanter		Lived 10 mos.
40816	W	F	48	Undetermined	All ribs, dorsal spine, lumbar spine, cervical spine, ilium, scapula, clavicles, humeri, femora		Irradiated and lead	
40734		F		Undetermined	Skull, pelvis, thoracic vertebrae, femur, ribs	Ribs, femur		Lived 15 mos.
39914	W	M	60	Undetermined	Right humerus, left humerus, spine	Right humerus	Irradiated	
30816	W	M	21	Undetermined	Skull, upper third of right femur	Upper third of right femur	Irradiated	Lived 30 mos.
30106	W	F	66	Undetermined	Ilium, left acetabulum	Ilium	Irradiated	Lived 27 mos.
39325		M	21	Sarcoma	Right temporal bone			
37465	W	M	42	Undetermined	Shaft, humerus and right femur			Lived 48 mos.
37890	W	F	70	Undetermined	Upper third of left femur	Femur		
36178	W	F	59	Carcinoma	Middle third of right femur	Femur	Amputation of right leg	Lived 18 mos.
36119	W	M	49	Carcinoma	Shaft of femur	Femur	Curettement	Lived 24 mos.
35828				Undetermined	9th dorsal vertebra, rib, femur			
33618	W	F		Undetermined	Upper third of left femur, tibia, fibula, left pubic bone	Femur	Irradiated	Lived 21 mos.
35310	W	M		Undetermined	Humerus		Prophylactic toxin treatment, biopsy and amputation	Living 45 mos. 1928
35702	W	M	29	Undetermined	Pelvis, 4th lumbar vertebra			
34972	W	F	33	Carcinoma	Right clavicle		Irradiated	Lived 8 mos.
34200	W	M	67	Colloid carcinoma	Upper third of right humerus		Amputation of right arm	
34101	W	M		Carcinoma	Clavicle		Resection of tumor	

was reported well, seven years and six months after the onset of symptoms.

Other isolated examples of metastases from various primary tumors to bone are shown in Table 71

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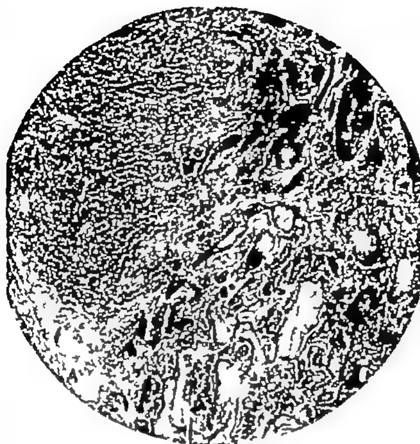
Smith, B T: Method for making a differential diagnosis between xanthomatous and melanin tumors from frozen sections, Arch. Surg. 8 908 1924

Spies* has collected a number of these cases. He found that the tumors are usually situated in the region of the nasopharynx, nasolabial fold, or about the buttocks, and that many of them metastasize after repeated recurrences.

BONE INVOLVEMENT IN NEUROBLASTOMA OF THE ADRENAL

In children under the age of five years a rare, malignant tumor may arise from undifferentiated nervous tissue found in the

Spies, J W: Adenoid cystic carcinoma; generalized metastases in 3 cases of basal cell type, Arch. Surg 21 365 1930.



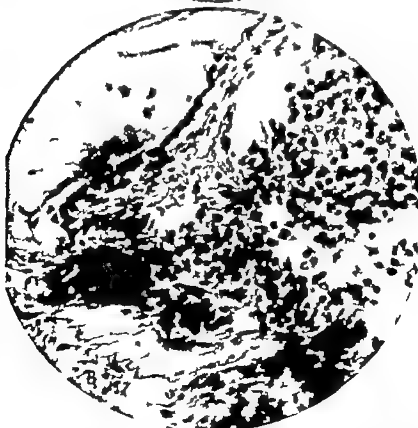


Fig. 369 (No 14500) Metastatic carcinoma of lung. (A) photomicrograph showing the d ction by direct contact with the tumor cells while in ar tempt is seen on the part of the bone to react by fib) high magnification of a bone icule being destr r Note the direct contact the tumor cel ld structure.

medulla of the adrenal. These tumors are variously known as neuroblastoma, sympathoblastoma or sympathicoblastoma. The clinical findings are usually produced by the metastases which may show a predilection for the liver (Pepper's syndrome) or for bone (Hutchinson's syndrome). Bone metastases from neuroblastoma of the adrenal are usually widespread and occur at an extremely early age. The tumors affect the skull, the pelvis and the long bones, producing small areas of resorption which in the long bones are on the shaft side of the epiphyseal line. The metastases are small or diffuse and are not accompanied by periosteal reaction (Fig. 373). Occasionally there is a characteristic wedge-shaped area of resorption above or below the epiphyseal line. The spine may be involved and the skull in the region of the calvarium rarely escapes. Exophthalmos may be produced by metastasis in the region of the orbit.

In the roentgenogram the bone involvement in children suffering from this disease must be differentiated from Christian Schüller's syndrome, chloroma, leukemia, Ewing's sarcoma and Wilms' tumor of the kidney (see Chapter 20). Particularly in lymphoid leukemia of the aleukemic type occurring in infants, the bone involvement may be practically indistinguishable in the roentgenogram from that produced by metastases in neuroblastoma. Rapid response to irradiation and a differential count of the white blood cells showing a relative lymphocytosis distinguish leukemia from neuroblastoma (Fig. 374).

In Christian's disease there are usually large circular defects in the skull, flat or long bones which respond to irradiation (Fig. 375). The patients are usually older (from 3 to 10 years) and soft-part tumors are palpable over the bones. Chloroma is most often found near puberty. Exophthalmos and lesions in the bones of the orbit may simulate the findings of neuroblastoma of the Hutchison type. Involvement of the other bones often shows a more definite



FIG. 370. Metastatic melanoma involving the lower end of the ulna, 11 years after the removal of the primary lesion.

periosteal reaction with palpable tumors in the soft parts. Tumors may also be found in the oral cavity or in the paranasal sinuses. In addition, there are the general signs and symptoms of leukemia and a response on the part of the tumor to irradiation.

Ewing's sarcoma of bone is not uncommon in children after the age of four. It is rarely reported earlier. It is most common in the long bones in which it produces longitudinal periosteal reaction with splitting of the subperiosteal and cortical layers in so-called onion-peel fashion. Involvement of other bones is seen only in terminal stages when metastases to the skull may occur. In such instances the skull involvement is accompanied by soft part tumors underlying the bony lesions. These masses also respond readily to irradiation.

Wilms tumor or malignant embryoma, of the kidney with bone involvement is ex tremely rare. In such cases the pelvis is usu ally eroded by direct extension, and the

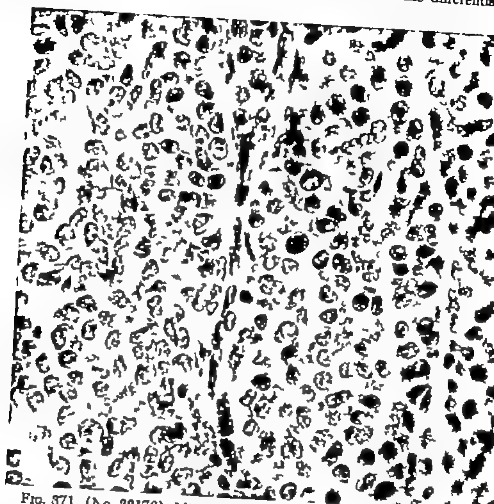


FIG. 371 (No. 32176) Microscopic picture of the tumor depicted in Figure 370 showing cells with the morphology of melanoma. Melanin pigment can be seen incorporated in many of the cells.

area of bone destruction is much larger than the metastatic foci seen in neuroblastoma.

METASTASES FROM AN UNDETERMINED MALIGNANT CONDITION

In many instances the clinician is unable to diagnose definitely the source of the lesion of the bone although a thorough examination has been made and roentgenograms of the entire skeleton examined. Even when a biopsy is taken, the morphologic structure of the cells in the microscopic picture are such that little more can be said than that a metastatic lesion is present.

There are thirty-one such laboratory and in none of the to determine the primary foc gen criteria in the differentia lesions of the bone, as pointed ou ously in this chapter (see sect breast) plus clinical and laboratory have usually aided in classifying th sions as metastatic to bone, though instances the true nature of the dis left unsolved (Tables 73 and 74)

Little can be gained from detailed ysis of this group. It is to be pointe however that many of these patients relieved from symptoms of pain for periods by the administration of roe therapy and in a few instances the pat lived from three to eight and a half y



FIG 372. (No. 40299) (A) and (B) show an invasion of the skull, pelvis and upper ends of the femurs from an adenoid-cystic, basal-cell carcinoma of the nasopharynx. Note the combined destruction and formation of bone within the areas of metastases.



FIG. 373A. (No 55657) Roentgenogram of the pelvis and humerus in a case of neuroblastoma of the adrenal with bone metastases.

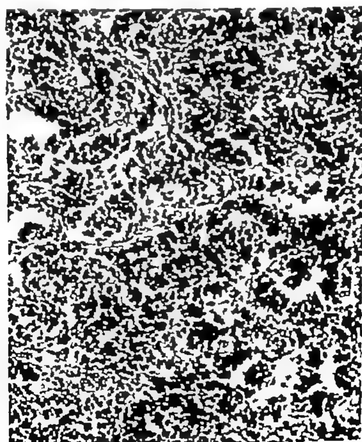


FIG. 373B. Photomicrograph of neuroblastoma shown in (A).

following roentgen therapy or amputation of the affected part

MODE OF METASTASIS

Since the time of Virchow and his fundamental work on tumors, many attempts have been made to explain secondary metastatic lesions. von Recklinghausen* was among the first to champion the theory of the spread of malignant tumors by the blood stream into the bone marrow and his deduction was based on the three following points 1 Metastases in bones occur within the medullary cavity and reach the periosteum only by extension from the interior 2. When the subperiosteal tissue is invaded, it is always in the region of the large foramina, which serve as a point of egress for the veins. 3. The individual cancer cells in the marrow lie within definite channels, which are arranged in a manner similar to that of the veins present in the marrow

Proof that the tumor cells lay within the small venous channels was based on the fact that von Recklinghausen could find no blood channels free from the tumor in the invaded areas, and that no known lymphatic

TABLE 74 INVOLVEMENT OF BONE IN THIRTY-SEVEN CASES OF AN UNDETERMINED PRIMARY MALIGNANT DISEASE

Bone Involved	Number of Cases	Number of Times	Right	Left	Undetermined Side
Pelvis					
Location (?)	2	2			2
Ilium	9	9	1	2	6
Ischium	1	2	1	1	
Pubis	1	1		1	
Sacro-iliac joint	1	1			1
Acetabulum	1	1		1	
Sacrum	1	1			1
Femur					
Location (?)	7	[illegible]	3	2	3
Upper third	5	5	1	3	1
Middle	3	3	2		1
Spine					
Location (?)	2	2			1
Cervical	4	4 (twice number not stated)			
Thoracic	5	5 (twice number not stated)			
Lumbar	3	2 (once number not stated)			
Clavicle.	8	8	5	3	1
Humerus					
Location (?)	5	[illegible]	2	2	2
Upper	2	2	2		
Middle	1	1			1
Lower					
Rib	7				
Skull	6	5	1	1	3
Tibia					
Location (?)	3	3	1	1	1
Upper	1	1	1		
Scapula	3	4	1	1	2
Fibula, location (?)	2	3	1	1	1
Phalanx.	1	1	1		1
Metatarsal	1	1	1		1

* Von Recklinghausen, F. Die Fibrose oder deformierende Ostitis, die Osteomalacie und die osteoplastische Carcinose in ihren gegenseitigen Beziehungen, Festschr. der Assistenten fur Virchow 1891, p. 17

increased, deposits of fat appeared in marrow but were not present in equal units in all of the bones In the adult, vertebrae sternum, pelvis and most of rib contained red cellular marrow the red marrow in the long bones of the bs being found in a small area at the er end of the diaphyses. The marrow of bones of the extremities as a major reason for the paucity of metastases in those regions

The work of Batson has confirmed the embolic theory According to Batson the vertebral veins are a valveless plexus which form a separate system or pool for blood forced out of the thoraco-abdominal cavity

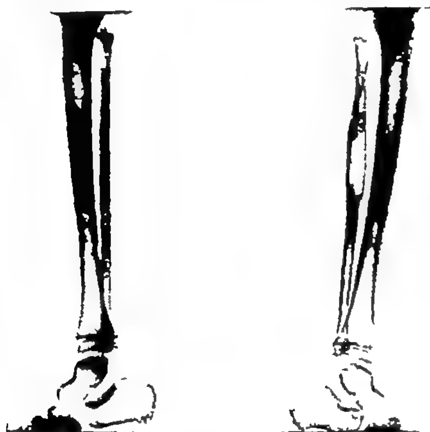


Fig. 375 (No 37070) Roentgenogram of Christian's disease in the left fibula in a boy of four

the small bones of the hands and feet showed complete conversion into fat at a much earlier date. In the bone marrow he was able to find vascular channels but no evidence of lymphatic vessels. In cases with metastases within the vascular channels, plugs of epithelial cells were found both in the bone marrow and at the sites where the veins emerged through the foramina—points at which carcinomatous metastases reached the surface These changes were cited by him as evidence in favor of the embolic theory He set forth the observation of lack of bone marrow in the small by any act of coughing, sneezing, lifting or straining He has demonstrated that material injected into the breast venules enters this vertebral system via the intercostal veins, and "duplicates the pattern of aberrant breast cancer spread, i.e., spread into the spine, the ribs, the shoulder girdle and the skull." Metastasis may therefore, be distributed anywhere along the vertebral system without involving the portal, the pulmonary or the caval system of veins. According to this concept, the system of communicating vertebral veins is "constantly and physiologically the site of frequent

reversals of flow During these reversals a pathway up and down the spine exists which does not involve the heart or lungs." These veins communicate with the veins of the brain and meninges and have connections with the veins of the body cavities at each intervertebral space.

These findings of Batson s indicate that the venous system is equally as important as the lymphatic system in explaining the dissemination of mammary and visceral cancers. Apparently most metastases to the osseous system or to the brain occur via the vertebral venous system described by Bat son In injecting a vein just lateral to the areola, the injection spread to the skin sur rounding the injection site and extended past the midline. Batson states the spread of injected material, in the sub-papillary plexus of the skin, indicates that Handley s lymphatic permeation theory even as it con cerns the skin, might be restudied with profit." The findings at autopsy in recent studies of metastasis in mammary cancer such as that of Warren and Witham, and of Turner and Jaffe, stress the importance of dissemination via the blood vessels.

Sampson Handley in a treatise on cancer of the breast, in 1906, presented the view that cancer is disseminated to bone by per meation of the lymphatics and was of the opinion that the majority of metastases to the bone occurred by direct extension of the tumor cells through the deep fascial lymphatics that both the humerus and the femur were invaded at points usually in the region where the bone lies nearest the deep fascia or at the point where it comes near est to the cutaneous surface, and that the bones beneath the knee and elbow were rarely involved, owing to a fatal termination of the case before the in[illegible] the lymphatics reached these di[illegible]ns.

Fol[illegible] is contrib[illegible] have be[illegible]ocates of [illegible]tion. Am[illegible] recent i[illegible] ar nett[illegible]ve supp[illegible]ry l[illegible]tion, w[illegible]

tion in the case of neoplastic extension within the abdomen they have found the cancer cells permeating the retroperitoneal lymphatics, and in no case have they found the extension of tumor by transcoelomic transplantations as was suggested by Handley This study is of particular interest in that complete roentgenographic studies were made of a large series of cases of mammary cancer showing metastases in the bone, and they have emphasized the fact that invasion seems to occur first in the region of the primary tumor with subse quent involvement of other bones in juxta position to those already invaded. How ever it must be noted that the majority of their cases were in the late stages of the disease, so that either operation was impossible or radical operation was deemed futile.

In the literature cases are recorded with the idea of establishing either the embolic or the lymphatic mode of metastasis, and in some instances pathologists, notably Ewing, have stated that both modes of transmission occur

In the analysis of carcinoma of the breast with metastases to the skeletal system in this laboratory certain facts are pertinent.

Clinically it was found that the majority of the patients had been treated by radical amputation of the breast early in the disease and thus many of the lymphatics which might have provided an avenue for tumor invasion were destroyed. This observation is borne out when one comes to study the incidence of bony involvement and finds that relatively few of the osseous metastases are in the immediate vicinity of the primary tumor

When the pelvic bones were involved, there was not infrequently an associated invasion of the heads of the femurs (Fig 346) and the gross and microscopic study in some of these instances showed direct inv[illegible] by means of the ligamentum te[illegible] stablishing further proof that th[illegible]ension of tumor from one bone

to another via the lymphatics as well as extension from the primary tumor to the regional bones by this route But when one studies the long bones, such as the humerus and the femur and less frequently the bones of the forearm and those below the knee, especially in the case of single lesions, and notes the absence of invasion in the intervening structures between the primary focus and the distant metastases, one is forced to the conclusion that metastases occur by way of the blood stream.

Other groups of primary lesions metastasizing to bone found in this study have substantiated the facts brought out in the analysis of lesions of the breast and in addition have emphasized in the roentgen and gross study the relation of the nutrient vessels to the metastatic lesions, as well as establishing proof that many bones are invaded by direct extension of the tumor through the lymphatics.

With these facts at hand, it would seem that one must accept both hematogenous and *lymphogenous metastases*, and that the particular circumstances of each individual case, such as the duration and the character of primary tumor together with the method of treatment, will often determine the character of metastases and the route of dissemination.

TABLE 75 METASTASES TO THE BONE

Primary Malignant Conditions	Number of Cases	Osseous Metastases		Pathologic Fracture		Patients Living Over Five Years	
		Number of Cases	Per Cent of Cases	Number of Cases	Per Cent of Cases	Number	Per Cent
Mammary carcinoma	1 914	100	5.2	16	16.0	1	1.0
Prostatic carcinoma	1,040	134	12.8	3	0.2	0	0
Carcinoma of the stomach	537	7	1.3	1	14.2	0	0
Colon and rectal carcinoma	497	3	0.6	1	33.3	0	0
Melanoma	169	3	1 77	1	33.3	1	33 3
Uterine carcinoma	89	5	5.6	0	0	0	0
Hypernephroma	63	22	34.9	10	45.4	1	4.5
Ovarian carcinoma	60	1	1 6	0	0	0	0
Testicular sarcoma	42	1	2.4	0	0	0	0
Carcinoma of the lung	24	4	16.6	1	25.0	0	0
Ovarian sarcoma	15	1	6.6	0	0	0	0
Malignant disease of thyroid	15	6	4.0	2	33.3	0	0
Testicular carcinoma	13	1	7 7	0	0	0	0
Undetermined malignant disease		37		15	40.5	2	5 4
Nasopharyngeal carcinoma		1		0	0	0	0
Squamous cell carcinoma		2		0	0	1	50.0
Sarcoma of the soft part		2		0	0	0	0
Carcinoma of the bladder		1		0	0	0	0
Esophageal carcinoma		1		0	0	0	0
Iliac sarcoma		1		0	0	0	0
Carcinoma of the liver		1		0	0	0	0

SUMMARY

In 100 cancers of breast *with secondary* involvement of bone the primary lesions were found microscopically to be of the scirrhus type (58) with a few instances of adenocarcinoma (6) *medullary* carcinoma (4) comedocarcinoma (3) and colloid carcinoma (2) In one patient, the primary lesion was *found* to be fibrosarcoma.

The bones most often involved were, in the order of *frequency* the *spine* pelvis, *femur* skull, ribs and humerus, while metastases in the forearm and the lower leg were of infrequent occurrence.

Clinically pain of a severe rheumatic character was an important feature. When the metastatic foci were located about the spine, girdle pains and many other neurologic manifestations developed. Occasionally pain preceded roentgenologic evidence of skeletal metastases from 3 to 18 months. The majority of the cases eventually showed a secondary type of anemia with its complications as the disease progressed. In an occasional case reported in the literature it was pointed out that a pseudo-pernicious type of anemia was present. The terminal phases of the disease were a progressive emaciation, usually with much pain. When the lungs were involved (19 cases) respiratory embarrassment with spitting of blood and paroxysms of coughing were added features of discomfort.

Pathologic fracture occurred in 15 instances, 13 being in the femur, one in the ilium and multiple fractures of the ribs in the other case.

As shown by the roentgenogram, metastatic lesions of the bone from carcinoma of the breast were found most often to be multiple, presenting themselves as a single focus in only one-fourth of the cases. The majority of the solitary foci were in the vertebrae or femur. Two types of metastatic lesions were discussed (osteolytic and osteoplastic). The osteolytic form of metastatic deposit appeared to be the more common, and in the long bones both types were often found well above the usual entrance of the nutrient artery in the case of the femur and above or below it in the case of the humerus. Mottling representing an increase in the density of the bone was often found within the areas of destruction, together with thickening of the cortex above or below the site of metastasis, and it was pointed out that microscopically this proved to be an attempt at osseous repair of fibro-ostosis.

TABLE 76

Metastatic from prostate	134
Metastatic from breast	100
Metastatic hypernephroma	22
Metastatic from gastro-intestinal tract	11
Metastatic from female genitalia	7
Metastatic from thyroid	6
Metastatic from skin	5
Metastatic from lung	4
Metastatic from biliary tract	3
Metastatic from nasopharynx	2
Metastatic from bladder	1
Metastatic from chest wall	1
Metastatic from neck	1
Metastatic from testicle	1
Undetermined source	36
Total	334

Treatment has been emphasized, the patients being divided into three groups (1) those who first had a radical amputation of the breast, (2) those who had only simple amputation or local excision, and (3) those on whom no operation was performed and who received only various forms of palliative treatment. The results obtained from roentgen therapy were relief from pain in many instances and a definite prolongation of life. Resection of the affected part apparently had no effect on the duration of life, but gave relief from excruciating pain. Castration in women prior to the menopause by means of roentgen therapy and injections of testosterone propionate are valuable palliative measures.

Sixty-three cases of hypernephroma have been reviewed, and in 22 instances skeletal metastases were found. The bones usually affected, in the order of their frequency

were humerus, spine, femur pelvis, ribs, bones of the feet, skull and sternum.

The lesions of the bone appeared in the roentgenogram either as single or multiple foci, located in one or more bones. There was a single focus in a long bone in the majority of cases (59 per cent) It was pointed out that many of these lesions were at the site of the nutrient vessels, as well as in the heads of the femur and humerus, together with associated metastases of the pelvis in many cases. Little evidence was found, in metastases of the bone from hypernephroma, of any attempt at formation of new bone within the area of destruction

The evidence indicates a hematogenous route of metastatic invasion in hypernephroma. Irradiation alone offered as much for the prolongation of life in this group of cases as did surgical intervention alone or surgical measures combined with roentgen or radium therapy

Osseous lesions in carcinoma of the prostate were found in 134 of 1 040 cases and involved most frequently the pelvic bones, vertebrae and femurs. The patients showed obstructive urinary symptoms and enlargement of the prostate at the time the metastases were noted, with a subsequent progressive emaciation, secondary anemia and excruciating pain in the affected bones. In the roentgenogram, the metastatic lesions in the bones were predominantly osteoplastic, a characteristic phenomenon in bony deposits from prostatic cancer On gross examination, these metastatic areas were usually white or grayish nodules, surrounded and mixed with healing bone This reaction was found to be quite the reverse of that usually seen in other metastatic lesions, and apparently the invasive powers of the metastatic tumor were of such moderate character that the bone was allowed to proliferate with sufficient rapidity to keep apace with the invasion of the tumor Roentgen therapy offered relief from pain, but was not effective in eradicating the lesion or in greatly prolonging the life of the patient. Resection and amputation offered only comfort. Orchidectomy or the administration of estrogen pellets or both, are valuable palliative procedures.

Malignant disease of other organs with metastases to bone was found to be rare occurring in the incidence shown in Tables 75 and 76

It was pointed out that both an embolic and a lymphatic mode of involvement were responsible for metastatic lesions of bone.

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Osseous Changes in Diseases of the Bone Marrow and Lymphoid Tissue

HODGKIN'S GRANULOMA
LYMPHOSARCOMA
LYMPHATIC LEUKEMIA
MYELOID LEUKEMIA
CHLOROMA
ERYTHROBLASTIC ANEMIA
SICKLE-CELL ANEMIA
LIPOID GRANULOMATOSIS AND
RETICULO-ENDOTHELIOSIS OF BONE
XANTHOMATOSIS WITH CHOLESTEROLEMIA
GAUCHER'S SPLENOMEGALY
NIEMANN PICK DISEASE
CHRISTIAN-SCHULLER DISEASE
EOSINOPHILIC GRANULOMA
SARCOIDOSIS
RETICULOSIS, RETICULO-ENDOTHELIOSIS

In addition to the structural functions performed by osseous tissue, the skeleton houses and shields the hemopoietic system. These marrow elements along with lymphoid tissue and the phagocytic histiocytes or macrophages are derivatives of the primitive reticulo-endothelium. For this reason, the bone marrow is prone to reflect or participate in disturbances of the reticulo-endothelial system. The present chapter deals with the osseous changes which accompany diseases of the bone marrow lymphoid tissue and reticulo-endothelial system.

HODGKIN'S GRANULOMA

The bone marrow is more frequently involved in Hodgkin's granuloma than is suspected, as is shown by autopsy records. Ziegler found the marrow involved in 40 per cent of the cases, while Symmers noted medullary changes in 7 out of 15 cases These authors observed a proliferation of endothelial cells, fibrosis and, in some areas, an increase in normal cells of the bone marrow Other changes characteristic of Hodgkin's disease were present.

TABLE 77 INCIDENCE OF OSSEOUS CHANGES IN HODGKIN'S GRANULOMA AS REPORTED BY VARIOUS INVESTIGATORS

	Number of Cases	Cases with Osseous Changes	Per Cent
Baldridge and Awe	46	6	13.0
Uehlinger 1933	50	17	34 0
Barron	24	5	20 8
Kimpel and Belot	33	4	12.1
Dresser	149	16	10 7

Destruction of bone has been reported from time to time. Since the advent of the roentgen rays, groups of cases are available in which the earlier symptoms referable to the bones together with the roentgenograms can be studied, and the progress of the disease followed to its termination.

Clinical Study Of 396 cases of Hodgkin's granuloma studied by Craver and Copeland in the Memorial Hospital, the diagnosis was confirmed by biopsy or autopsy in 172. There were demonstrable changes in the bone in 27 cases, 15 7 per cent. The

TABLE 78 DATA ON TWENTY-SEVEN CASES OF HODGKIN'S GRANULOMA

Case	Age	Sex	Duration of Disease Prior to Osseous Change	Symptoms Related to Osseous Changes (Before and After Roentgenographic Evidence)	Demonstrable Visceral and Glandular Involvement	Osseous Involvement*	Microscopic	Treatment of Bones	Laboratory Findings	Duration of Life Following Osseous Change
1	34	M	4 yr., 4 mos.	Pain 1 yr. before; paralysis of right rectus muscle 8 mos. before	Left side of neck, left supraclavicular nodes, axillae, groins, mediastinum, retroperitoneal nodes, liver, spleen	Right femur diffuse (C); lumbar vertebrae 1, 2, 3, 4, 5 (C)	Hodgkin granuloma, fibrotic	Mixed low- and irradiated roentgen therapy, 12/7/30 to 12/30/30	Progressive secondary anemia	Dead; changes found at autopsy
2	40	M	3 yr., 1 mo.	Pain in bone 1 yr. before; spine rigid 1 yr. before	Right cervical node, left axilla, both groins, mediastinum	Thoracic vertebrae 11, 12 (C); lumbar vertebra 1 (C); after treatment (B)	Hodgkin granuloma, cellular	Irradiated roentgen therapy, 4/20/30 to 10/2/30	Moderate secondary anemia; Bence-Jones bodies negative	Living after 3 yr.
3	34	M	4 yr.	Pain 10 mos. before spinal changes; flaccid paralysis 2 mos. before	General glandular enlargement; spleen palpable	Thoracic vertebrae 11, 12 (B); lumbar vertebra 1 (B)	Hodgkin's granuloma	Radium emanation pack; Irradiated roentgen therapy 3/22/28 to 10/16/28	Marked secondary anemia	Dead after 4 mos.
4	43	F	8 yr., 10 mos.	Pain 3 yrs., 10 mos. before; rigidity of spine 6 mos. after	Bilateral cervical nodes, lateral right breast, left axilla, right groin, retroperitoneal nodes	Lumbar vertebrae 2, 3, 4 (B) with transverse processes (C); lumbar vertebra 3, partial collapse; left sacro-iliac region (B)	Hodgkin granuloma, sarcomatous	Roentgen therapy, 6/30/30 to 12/2/30	Slight leukocytosis; normal red blood count and hemoglobin	Lost after 2 yr., 5 mos.
5	47	M	2 yr.	Pain 2 wks. before; abdominal pain 7 mos., 3 wks. before; intestinal symptoms 5 mos. before; signs of cord compression 4 mos. after	Right axilla, right and left cervical nodes, inguinal regions, retroperitoneal nodes attached to vertebrae, mediastinum	Thoracic vertebra 9 (C) with collapse; sacrum (C); left 6th rib (C); pathologic fracture	Hodgkin granuloma, cellular	Roentgen therapy	Progressive secondary anemia	Dead after 7 mos.

6	17	F	5 yr. 4 mos.	Pain 2 mos. before signs of cord compression 2 yrs., 1 mo. after; rigidity of spine 1 yr. 2 mos. after	Left supraclavicular nodes, suprasternal nodes, mediastinum, groin	Cervical vertebra 6 (C); lumbar vertebrae 2, 3, 4 (C) with collapse; lumbar vertebra 5 (B); transverse process of lumbar vertebrae 3, 4, 5 (C); right 12th rib (C)	Hodgkin's granuloma	Radium therapy 4/17/25 to 12/14/26; radium emanation pack, 8/15/26 to 8/28/26	Marked secondary anemia	Dead after 2 mos.
7	17	F	1 yr. 4 mos.	Pain in lumbar region 7 mos. before signs of cord compression 6 mos., 2 wks. after	Left and right cervical nodes, axillae	Lumbar vertebrae 1, 2, 3 (C); transverse process of lumbar vertebra 2 (C); left ilium near crest (C); right and left [illegible] joint [illegible] (C); right [illegible] (C)	Hodgkin's granuloma	Irradiated roentgen therapy 1/8/33 to 4/12/33	Moderate secondary anemia and leukocytosis Bence-Jones bodies negative	Living after 1 yr., 8 mos.
8	21	M	9 mos.	Pain; tumor 2 mos. after	Bilateral cervical nodes, right axilla, spleen, retroperitoneal nodes, liver, stomach, peripancreatic pancreatic node	Right 6th rib (C and B)	Hodgkin's granuloma, cellular	Irradiated roentgen therapy 8/12/31 to 12/2/31; [illegible] therapy [illegible] [illegible] 3/11/33	Progressive secondary anemia and leukopenia	Dead after 6 mos., 2 wks.
9	[illegible]	F	2 yr. 10 mos.	Unsatisfactory data	Bilateral cervical nodes, axillae	Thoracic vertebrae 8, 9 (C) with collapse	Hodgkin's granuloma, cellular	Irradiated roentgen therapy radium emanation pack 9/20/33 to 12/8/33	Severe secondary anemia on admission with improvement after treatment	Dead after 2 yr., 1 mo.
10	26	F	3 yr. 7 mos.	Unsatisfactory data	Bilateral cervical nodes, axillary inguinal and mediastinal nodes	Thoracic vertebra 12 (C); lumbar vertebrae 1, 2, 3 (C) with collapse; osteoblastic reaction about collapsed area	Hodgkin's granuloma	Radium emanation pack, 8/17/31 to 8/22/31; injection of vaso tuberculin	Severe secondary anemia with marked leukocytosis, radium treatments and blood transfusions improved blood picture	Living after 1 yr.

Tables 78, 79 and 80 Previously published by Craver and Copeland

Table 78. Data on Twenty-Seven Cases of Hodgkin's Granuloma

Case	Age	Sex	Duration of Disease Prior to Osseous Change	Symptoms Related to Osseous Changes (Before and After Roentgenographic Evidence)	Demonstrable Visceral and Glandular Involvement	Osseous Involvement*	Microscopic	Treatment of Bones	Laboratory Findings	Duration of Life Following Osseous Change
1	34	M	4 yr., 4 mos.	Pain 1 yr. before; paralysis of right rectus muscle 8 mos. before	Left side of neck, left supraclavicular nodes, axillae, groins, mediastinum, retroperitoneal nodes, liver spleen	Right femur diffuse (C); lumbar vertebrae 1, 2, 3, 4, 5 (C)	Hodgkin granuloma, fibrotic	Mixed low- and irradiated roentgen therapy, 12/7/28 to 12/30/30	Progressive secondary anemia	Dead; changes found at autopsy
2	40	M	3 yr., 1 mo.	Pain in bone 1 yr. before; spine rigid 1 yr. before	Right cervical node, left axilla, both groins, mediastinum	Thoracic vertebrae 11, 12 (C); lumbar vertebra 1 (C); after treatment (B)	Hodgkin's granuloma, cellular	Irradiated roentgen therapy, 4/26/30 to 10/2/30	Moderate secondary anemia, Bence-Jones bodies negative	Living after 3 yr.
3	34	M	4 yr.	Pain 10 mos. before spinal change; flaccid paralysis 3 mos. before	General glandular enlargement, spleen palpable	Thoracic vertebrae 11, 12 (B); lumbar vertebra 1 (B)	Hodgkin granuloma	Radium emanation pack; irradiated roentgen therapy 8/22/28 to 10/16/28	Marked secondary anemia	Dead after 4 mos.
4	46	F	3 yr., 10 mos.	Pain 3 yrs., 10 mos. before; rigidity of spine 6 mos. after	Bilateral cervical nodes, lateral right breast, left axilla, right groin, retroperitoneal nodes	Lumbar vertebrae 2, 3, 4 (B) with transverse processes (C); lumbar vertebra 3, partial collapse; left sacro-iliac region (B)	Hodgkin granuloma, sarcomatous	Roentgen therapy, 6/30/28 to 12/2/30	Slight leukocytosis; normal red blood count and hemoglobin	Lost after 2 yr., 5 mos.
5	27	M	3 yr.	Pain 2 wks. before; abdominal pain 7 mos., 2 wks. before; intestinal symptoms 6 mos. before; signs of cord compression 4 mos. after	Right axilla, right arm, left cervical nodes, inguinal regions, retroperitoneal nodes attached to vertebrae, mediastinum	Thoracic vertebra 9 (C) with collapse; sacrum (C); left 6th rib (C); pathologic fracture	Hodgkin granuloma, cellular	Roentgen therapy	Progressive secondary anemia	Dead after 7 mos.

6	17	F	3 yr. 4 mos.	Pain 2 mos. before signs of cord compression 2 yrs., 1 mo. after; rigidity of spine 1 yr., 3 mos. after	Left supraclavicular nodes, suprasternal notch, mediastinum groin	Cervical vertebra 6 (C); lumbar vertebrae 2, 3, 4 (C) with collapse; lumbar vertebra 5 (B); transverse process of lumbar vertebrae 3, 4, 5 (C); right 12th rib (C)	Hodgkin's granuloma	Radium therapy 4/17/28 to 12/14/28; radium emanation pack, 4/15/29 to 5/22/29	Marked secondary anemia	Dead after 3 mos.
7	17	F	1 yr. 4 mos.	Pain in lumbar region 7 mos. before; signs of cord compression 6 mos. 3 wks. after	Left and right cervical nodes, axillae	Lumbar vertebrae 1, 2, 3 (C); transverse process of lumbar vertebra 2 (C); left ilium near crest (C); right and left sacroiliac joint regions (C); right [illegible] (C)	Hodgkin granuloma	Irradiated roentgen therapy 1/6/33 to 4/12/33	Moderate secondary anemia and leukocytosis Bence-Jones bodies negative	Living after 1 yr., 3 mos.
8	27	M	9 mos.	Pain; tumor 2 mos. after	Bilateral cervical nodes, right axilla, spleen, retroperitoneal nodes, liver, stomach, perigastric pancreatic nodes	Right 6th rib (C and B)	Hodgkin's granuloma, cellular	Irradiated roentgen therapy 9/12/31 to 12/3/31; Heublein unit therapy 15% [illegible] 3/11/32	Progressive secondary anemia and leukopenia	Dead after 9 mos., 3 wks.
9	27	F	2 yr. 10 mos.	Unsatisfactory data	Bilateral cervical nodes, axillae	Thoracic vertebrae 8, 9 (C) with collapse	Hodgkin granuloma, cellular	Irradiated roentgen therapy radium emanation pack 9/29/33 to 12/6/33	Severe secondary anemia on admission with improvement after treatment	Dead after 2 yr., 1 mo.
10	30	F	3 yr. 7 mos.	Unsatisfactory data	Bilateral cervical nodes axillary inguinal and mediastinal nodes	Thoracic vertebra 12 (C); lumbar vertebrae 1, 2, 3 (C) with collapse; osteoblastic reaction about collapsed area	Hodgkin granuloma	Radium emanation pack, 2/17/31 to 2/23/31; injection of avian tuberculin	Severe secondary anemia with marked leukocytosis; radium treatments and blood transfusions improved blood picture	Living after 1 yr.

Tables 78, 79 and 80 Previously published by Craver and Copeland

TABLE 78. DATA ON TWENTY-SEVEN CASES OF HODGKIN'S GRANULOMA (*Continued*)

Age	Sex	Duration of Disease Prior to Osseous Change	Symptoms Related to Osseous Changes (Before and After Roentgenographic Evidence)	Demonstrable Visceral and Glandular Involvement	Osseous Involvement	Microscopic	Treatment of Bones	Laboratory Findings	Duration of Life Following Osseous Change
32	M	1 yr 6 mos.	Unsatisfactory data	Left cervical nodes, mediastinum, right cervical node, axillae	Right ilium, mid-portion (C), left ilium near sacro-iliac margin (C); area about acetabulum involved	Hodgkin granuloma	Irradiated roentgen therapy 11/20/31 to 4/11/32	Moderate progressive secondary anemia; initial marked leukocytosis; transition toward normal count	Dead after 1 yr., 9 mos.
41	M	2 yr	Unsatisfactory data	Right and left supraclavicular nodes, axillae mediastinum	Lumbar vertebra 5 (B) with transverse process (C); sacrum (B) near sacro-iliac joints; right innominate central (C); left ilium central (C)	Hodgkin granuloma, cellular	Irradiated roentgen therapy 3/31/30 to 2/30/32	Initial leukocytosis reverting to normal	Living after 11 mos.
20	M	1 yr 2 mos.	Pain 1 yr., 3 wks. before	Left cervical nodes, axillae, over left clavicle and right scapula	Frontal bone (C); lumbar vertebrae 1, 2, 3, 4, 5 (B)	Hodgkin granuloma	Irradiated roentgen therapy 1/31/31 to 8/25/31 Hodgkin's serum therapy 20 cc., 6 E.D., 2/27/32	Moderate secondary anemia following Hodgkin therapy; transfusion followed by leukocytosis and increase in red count. Bence-Jones bodies negative	Living after 7 mos., 2 wks.
17	M	1 yr 4 mos.	Pain in pelvis 20 days before, pain in upper tibia 4 mos., 2 wks. before; tumor in region of left buttock 8 mos. after	Mediastinum, left and right cervical nodes, inguinal nodes, spleen	Right ilium near sacro-iliac joints and wings (B); ischia (B); pubes (B); tibia (C)	Hodgkin granuloma; some fibrosis	Irradiated roentgen therapy 7/18/30 to 2/16/32	Admitted with moderate secondary anemia and normal white blood count; anemia improved and leukocytosis developed	2 yr., 8 mos., dead
40	F	2 yr 6 mos.	Pain 8 mos. before in left ilium, (?) pain a few weeks before in right ilium	Right cervical nodes, right supraclavicular nodes, axillae, inguinal nodes	Left ilium (C); right ilium (C); left femur (C); thoracic vertebrae 4, 5 (C)	Hodgkin granuloma, cellular	Irradiated roentgen therapy 3/1/30 to 11/9/31	Unsatisfactory data	Dead after 2 yr., 2 wks.
19	M	1 yr 4 mos.	Tumor 13 mos., 2 wks. before roentgenogram was made	Left upper lung, mediastinum, left and right cervical nodes, axillae, spleen	Left 2d rib (C)	Hodgkin granuloma, fibrotic	Radium emanation pack, 4/17/[illegible] to 5/15/[illegible]; irradiated roentgen therapy, 9/14/30 to 9/[illegible]/30	Normal red blood count and hemoglobin; moderate leukocytosis; normal toward end of life	Dead after 1 yr., 9 mos.

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17	23	M	1 yr 6 mos	Abdominal pain 8 mos 21 days before pain in spine 9 mos 3 wks. before; pain in left humerus 4 mos 2 wks. before signs of cord compression 3 mos after	Left cervical nodes, spleen	Thoracic vertebrae 11 12 (B) lumbar vertebrae 1 3 (B) left humerus (C)	Hodgkin granuloma, cellular	Irradiated roentgen therapy 9/10/26 to 8/14/29	Moderate secondary anemia	Dead after 1 yr 3 wks.
18	24	M	8 mos	Pain 7 mos. before symptoms of cord compression 3 wks. after	Mediastinum, right and left supraclavicular nodes, axillae groins, spleen liver	Left humerus (C); lumbar vertebra 2 ith transverse process (C); lumbar vertebrae 4 5 (B)	Hodgkin granuloma	Irradiated roentgen therapy 4/10/29 to 12/26/29; 3 transfusions	Marked secondary anemia with some improvement nor mal white blood count, on one occasion low; transfusion treatment	Dead after 9 mos 3 wks.
19	29	F	8 5 3 mos	Pain 10 mos before in right femur pain 1 mo. before in left femur pain 1 yr, 6 mos before in pelvis	Mediastinum, left and right cervical nodes, right supraclavicular nodes, spleen	Left femur upper third (C) left femur mid-shaft (B); ilia about sacro-iliac joints (C); right femur upper third (C)	Hodgkin granuloma; some fibrosis	Irradiated roentgen therapy 10/22/28 to 4/29/31; 1 transfusion	Progressive secondary anemia; intermittent leukocytosis; anemia improved after treatment and transfusion	Dead after 1 yr., 7 mos.
20	21	F	1 yr 3 wks	Pain in femurs 8 mos before, pain in upper left tibia 2 mos 2 wks before; pain in left side of abdomen 3 mos. before changes in left ischium	Mediastinum left and right cervical nodes, right axilla spleen	Left and right femur C); left tibia (C)	Hodgkin granuloma	Irradiated roentgen therapy 4/3/29 to 10/2/29	Progressive secondary anemia	Dead after 2 mos., 3 wks.
21	40	F	3 yr 1 mo.	Unsatisfactory data	Mediastinum right and left cervical nodes, right and left supraclavicular nodes, axillae, spleen	Lumbar vertebrae 1 2 3, 4, 5 (B); pelvic bones (B); right and left femur (C)	Hodgkin granuloma, cellular	Irradiated roentgen therapy 3/14/42 to 3/23/42 tuberculin injections	Slight leukocytosis, urine and Bence-Jones bodies negative	Living after 1 yr

TABLE 78. DATA ON TWENTY-SEVEN CASES OF HODGKIN'S GRANULOMA (*Continued*)

Case	Age	Sex	Duration of Disease Prior to Osseous Change	Symptoms Related to Osseous Changes (Before and After Roentgenographic Evidence)	Demonstrable Visceral and Glandular Involvement	Osseous Involvement	Microscopic	Treatment of Bones	Laboratory Findings	Duration of Life Following Osseous Change
22	16	F	5 mos.	Pain in left humerus 5 mos. before; pain in right upper humerus 9 mos. after; pain in upper tibia 1 yr before	Mediastinum, left supraclavicular nodes, left axilla	Left humerus (C); right humerus (C); left 6th rib (C); pathologic fracture 6th rib	Hodgkin granuloma; some fibrosis	Irradiated roentgen therapy 10/22/31 to 3/11/32; Heublein unit therapy, 25% S.E.D.†, 4/6/32	Moderate secondary anemia; terminal leukocytosis; Bence-Jones bodies negative	Failing after 7 mos., 2 wks.
23	27	M	2 yr 7 mos.	Signs of cord compression 7 mos., 1 wk. before pain 6 mos., 1 wk. before in vertebrae	Mediastinum, right and left cervical nodes, right axilla, spleen, groins, mesenteric glands	Thoracic vertebrae 10, 11 (B); right ischium, right pubis (C)	Hodgkin granuloma, cellular	Irradiated roentgen therapy to general regions not specifically directed to bones	Moderate leukocytosis	Living after 1 yr 1 mo.
24	31	F	4 yr 6 mos.	Pain immediately before	Mediastinum, right supraclavicular nodes, axillae, groins	Frontal bone (C)	Hodgkin granuloma	Irradiated roentgen therapy 9/26/30 to 10/2/30; Heublein unit, 6/6/32	Blood, no abnormal change; Bence-Jones bodies negative	Living 9 mos. 2 wks.
25	57	F	2 yr 8 mos.	Tumor 4 mos. before	Mediastinum, left and right cervical nodes, right axilla, right inguinal nodes	Sternum, lower third (C and B)	Hodgkin granuloma, cellular	Heublein unit therapy 15% S.E.D.; 1 irradiated roentgen treatment	Moderate progressive secondary anemia, intermittent leukopenia	Living after 4 mos., poor condition
26	43	F	4 yr 2 mos.	Unsatisfactory data	Mediastinum right and left cervical nodes	Parietal bone (C)	Hodgkin granuloma	Erysipelas and prodigiosus toxins (Coley's)	Moderate leukocytosis	Dead after 1 yr., 6 mos.
27	30	M	10 yr	Unsatisfactory data	Right and left cervical nodes, tonsils	Right ribs 1, 2, 3, 4 near sternum (C)	Hodgkin granuloma	Radium emanation pack, 9/17/23 to 9/22/23; low voltage therapy, 11/9/23 to 3/13/24 and 11/12/24 to 1/19/25	Unsatisfactory data	Living after 5 mos., 1 wk.

* Osteoclastic involvement is indicated by (C), osteoplastic, by (B)
† S.E.D. indicates skin erythema dose

incidence of bone changes in this group may be compared with that reported by other authors in Table 77 The variable duration of Hodgkin's granuloma before and after definite invasion of the bone is shown in Table 78. Eleven patients were living with changes which had existed from four months to three years. In the patients who died, skeletal changes were noted from two months to two years prior to death.

In the present series the ages of the patients affected by Hodgkin's disease with associated osseous changes varied from 16 to 57 years. The ratio of males to females was two to one. Pain preceded demonstrable invasion of the bone in 17 cases. It was of a dull aching or severe and lancinating quality produced by either invasion of the nerve roots, by pressure on the nerve or by the destruction of the bone. Pain was frequently referred from the lumbar region to the lower extremities, and was accentuated by changes in posture. Girdle pains were experienced with vertebral changes. The interval between the beginning of pain and the demonstration of osseous changes extended from a few days to three years.

In many cases roentgenograms were made periodically and only after a considerable time had elapsed were changes in the density of the bone noted. Frequently the bones in regions without symptoms showed roentgenographic changes.

Pain, rigidity of the spine and localized tenderness were observed, associated with vertebral changes and compression of the cord. In five patients compression of the cord occurred from three weeks to two years after appearance of vertebral changes. Roentgen therapy was effective in ameliorating these spinal symptoms.

In one case a lesion of a rib was found by routine roentgenographic examination two months before pain and swelling were observed. In two patients herpes zoster appeared on the left side of the chest. In neither patient were lesions demonstrated in the thoracic vertebrae, but both had large mediastinal masses. The cause of herpes zoster has been variously ascribed to infiltration or compression of the nerves or to toxic substances reaching the nerves by circulatory paths (Voorhoeve)

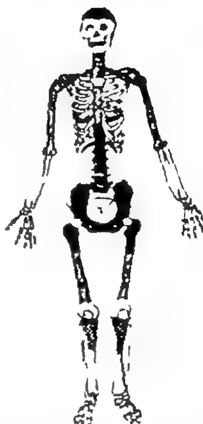


FIG. 376 Diagram showing the distribution of Hodgkin's granuloma in the skeleton. The black areas represent the most frequent sites, the checkered areas, the common sites; the diagonal lines, the occasional areas, and the white areas, the rarely invaded portions of the bones.

Referred abdominal pain in three cases was traced to diseased vertebrae impinging on nerves, or to large retroperitoneal nodes disturbing the function of the stomach.

Fever accompanied by a slight albuminuria was frequently present in those cases in which the disease affected bone. Though a search for Bence-Jones bodies in the urine was not a routine procedure, they were not found in the four cases in which tests were made. Galloway reported the presence of a Bence-Jones like protein

in the urine of a patient with Hodgkin's granuloma, whose kidneys were involved. No mention was made of the condition of the bone marrow

terially alter the blood picture from that generally seen in the disease. The white cell count varied from leukopenia to marked leukocytosis. In 20 cases, from 1 to 6



FIG. 377 A roentgenogram showing Hodgkin's granuloma invading both the left and the right femurs. The lesions of the left femur simulated Garré's osteomyelitis with thickening of the cortex, a proliferation of the periosteum and a tendency to obliterate the marrow cavity The right femur in its upper portion shows a small area of central destruction with some thickening of the medial cortex and a slight periosteal reaction about the area of involvement.

A marked secondary anemia was present in some cases. Improvement in the anemia followed irradiation of the diseased bones or lymph nodes, unless the marrow received a dose of roentgen therapy which temporarily inhibited the formation of blood. Osseous involvement did not ma-

eosinophils were observed in individual blood counts. Leukopenia, when present, usually followed substantial irradiation. A leukocytosis was often reduced to a relatively normal level by irradiation The treatment causing a reduction in the white blood cells was not always directed toward the

osseous system. The terminal phases of the disease revealed a progressive emaciation and anemia.

Involvement of Bone A review of the literature indicates that vertebral changes are most frequent. The bones involved in the order of their frequency were vertebrae sternum, pelvis, femur ribs, skull, humerus, scapula and clavicle. Few reports dealt with lesions of other bones. Among our patients the bones most often affected were those of the spine and pelvis (Fig. 376) Pathologic fracture was rare but collapse of the diseased vertebrae was common.

The osseous lesions as depicted by roentgenograms are either osteoplastic (Fig 377) or osteoclastic (Fig 378) In the long pipe bones the involved portion was usually situated near the proximal end. As the disease progressed, the entire bone was frequently involved Since Hodgkin s granuloma involves chiefly the hematopoietic tissues, the reason for this distribution of osseous invasion is apparent At birth all of the skeleton except the cranium contains red marrow but with age fatty deposits replace the marrow gradually leaving red marrow in the long bones only at the upper ends of the diaphyses. The vertebrae, sternum, pelvis and most of each rib retain their red marrow in adults.



FIG 378. Roentgenogram showing destruction of the head of the humerus in lymphatic leukemia. Note the pathologic fracture and partial collapse Below the area of destruction small areas of rarefaction may be seen in the shaft. The periosteum is lifted by the disease process and gives an appearance somewhat similar to the onion-peel formation seen in Ewing s tumor

Progression of the disease accentuated the varieties of osseous changes already mentioned. In many cases, destruction of bone and the production of new bone accompanied each other

Roentgenograms of the skull presented a predominant osteolytic reaction. The areas of destruction were surrounded by varying degrees of increased density representing new bone (Fig 379) The sternum, close to involved mediastinal nodes, occasionally showed a marked periosteal reaction with cortical destruction of the bone. Destructive lesions of the ribs resembled other metastatic processes.

The vertebrae showed complete destruction with partial collapse or appeared sclerosed, with or without collapse. Several neighboring vertebrae were usually affected. *Sclerosis of the vertebral bodies and* osteolytic changes in the transverse processes were sometimes depicted in the same roentgenogram. As many as three or four vertebrae were found partially collapsed, one on the other suggesting disappearance of one or two vertebrae (Fig 381) Dresser who has made a study of this feature, found that the intervertebral disks were intact despite the fact that the bone was destroyed about them. Uehlinger found that the intervertebral disks were sometimes crushed and broken. The periosteum of the vertebrae was frequently raised. The subperiosteal proliferation varied in amount and was often associated with collapse of the vertebrae.



Fig 379 (No 54134) Roentgenogram showing multiple defects in the skull in a case of Hodgkin's disease of bone and liver without involvement of lymph nodes or spleen. (Herscher H.: Am. J Roentgenol. 35: 73.)

The pelvis may be involved by extension of the disease from neighboring lymph nodes. The lesions usually appear in the wings of the ilia or about the sacro-iliac joints. Osteolytic areas are surrounded by *areas of increased* density

Pathology A histopathologic study of the lymph nodes showed varying stages of Hodgkin's granuloma. Marked fibrosis, sarcomatous features or more often typical changes characterized by endothelial giant cells (Reed-Sternberg cells) proliferating endothelium and infiltration by eosinophils

were seen. Unfortunately the biopsy speci mens usually were not taken at the time the lesions of the bone were first observed.

Complete autopsy was performed in five cases. The diseased lumbar vertebrae were removed and on cross section showed discrete and confluent patches of Hodg kin s granuloma the process infiltrating the spongy portion of the vertebrae. No periosteal reaction was seen. The intervertebral disks were not involved. One rib showed lifted periosteum with proliferation of granulomatous tissue beneath it. A central destructive area was noted with some reactive bone about it. Diseased tissue beneath the periosteum coalesced with the reactive bone. The marrow from the verte brae and femur of the same case showed mucinous degeneration but no evidence of Hodgkin s disease. The marrow in the rib near the lesion was in large part replaced by the disease process (Fig 381)



Fig. 380 (No. 54134) Roentgenogram of the pelvis showing destruction and pathologic fracture in the left ischium, from the same case shown in Figure 379

Treatment Irradiation is the most effective therapy in Hodgkin s disease. In general, it appears that patients do not tolerate well a routine heavy irradiation of all the lymph node areas, and, on the other hand, failure to secure satisfactory palliation may follow neglect of treatment of certain areas such as those containing the deeper nodes.

The lesions of the bones may be treated to good advantage either by single large suberythema doses or by fractional doses of high-voltage roentgen rays. Relief from pain is often prompt, and reparative proc esses may be demonstrated in some cases. In the terminal stages, however routine irradiation of all the bones is not attempted, although it is well known that the marrow is diffusely involved. In such cases a severe degree of anemia and sometimes leukopenia already exists and would only be aggra vated by irradiation

While irradiation is still the treatment of choice in Hodgkin s disease, several other forms of palliative therapy are of benefit in cases which do not respond to this treat ment. Among the newer forms of treat ment are nitrogen mustard intravenously and oil-soluble nickel octyl-phthallate and

radioactive calcium in minute doses. The authors have not seen relief of bone symptoms with nitrogen mustard, but relief of pain and partial healing have occurred with radioactive calcium. The oil soluble nickel is more advantageous with lymph node and visceral involvement than it is with bony involvement.



FIG. 381 Roentgenogram showing marked destruction of the third and fourth lumbar vertebrae. Partial collapse of the vertebrae is noted. Periosteal proliferation together with some formation of new bone is seen. There is increased density of the fifth lumbar vertebra. The transverse processes of the fifth lumbar vertebra show osteolytic involvement.

LYMPHOSARCOMA

Bone involvement in lymphosarcoma is rare. In the records of the Memorial Hospital analyzed by Craver and Copeland, one hundred and sixty-four cases in which the diagnosis of lymphosarcoma was established by biopsy or at autopsy were found. Seventeen patients (10.4 per cent) were found to have involvement of the bone (Table 79)

While the duration of lymphosarcoma before and after the involvement of the bone is variable, the total duration of the disease is shorter than that usually seen in Hodgkin's granuloma. Most of the patients died before the third year of the disease. Two living patients had skeletal invasion which has existed for a year. In the patients who died, demonstrable changes in bone were noted from twenty days to one year prior to death.

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Clinical Features. The patients were usually past the age of 20 years. There were two children aged 9 and 11. Pain was an early symptom of involvement of bone in 11 cases. It could be accounted for by pressure on the nerves or by destruction of the bone. The pain was not infrequently referred down the arm or leg. Girdle pain was occasionally recorded. Involvement of the mandible simulated toothache. Pain in the lower part of the abdomen was a feature in one case. This was followed by symptoms of compression of the cord. The interval between the beginning of pain and the occurrence of demonstrable osseous changes varied from three months to two years. In one patient, signs of compression of the cord occurred five months after the appearance of osseous changes in the first, second and third dorsal vertebrae. Extensive herpes zoster was observed about the right shoulder girdle five months previously.



FIG. 362. A photomicrograph showing Hodgkin's disease invading the haversian canal of a rib. Endothelial giant cells are present in large numbers. Many plasma cells and eosinophils are seen. The bone shows erosion with no tendency to the formation of new bone.

The blood picture was usually that of

TABLE III LYMPHOSARCOMA

Case	Age	Sex	Duration of Disease Prior to Change in Bones	Symptoms Related to Changes in Bones (Before and After Roentgenographic Evidence)	Demonstrable Involvement of Viscera and Nodes	Involvement of Bones*	Microscopic Examination	Treatment of Bones	Laboratory Observations	Duration of Life Subsequent to Changes in Bones
1	50	F	2 years, 6 months	Tingling sensations in fingers of right hand 1 year and 11 months before; pain in right hip 7 months before	Left femoral triangle, above left Poupart's ligament, right groin, infiltration of left cheek	Skull (C and P); right upper part of humerus (C); right scapula (C); pelvis (C); femora (C)	Reticulum cell lymphosarcoma	Irradiated roentgen therapy 12/5/40 to 6/19/31	Progressive secondary anemia; eosinophilia present	Died after 8 months, 2 weeks
2	19	F	1 year	Pain in left arm and back 6 months before; symptoms of compression of the cord 6 months before	Left cervical nodes, supraclavicular fossa, left axilla, left inguinal nodes, sternal nodes	Skull (C); left humerus (C); dorsal vertebra 12 (P); lumbar vertebrae 4, 5 (C and P); pelvis (C and P); femora (C); bilateral pathologic fracture; tibiae (C and P); left fibula (C)	Reticulum cell lymphosarcoma	Radium emanation pack, small doses 1/7/32 to 1/8/32; irradiated roentgen treatments; erysipelas and prodigiosus toxins (Coley's); transfusions	Marked secondary anemia, improved by transfusions	Died after 2 months
3	34	F	3 years	Pain in lumbar region 2 years before	Right axilla, deformity of stomach, splenic enlargement, mediastinum	Lumbar vertebra 2 (P)	Reticulum cell lymphosarcoma	Roentgen therapy	Moderate progressive secondary anemia; eosinophilia present	Died after 1 year
4	40	M	9 months	Pain in right pubic bone 9 months before; swelling of right groin 9 months before	Cervical nodes, right groin, liver enlarged, mediastinum	Right pubic bone (C)	Lymphosarcoma	Irradiated roentgen therapy 6/27/31 to 9/10/31; radium emanation pack 7/21/31 to 8/2/31	Progressive secondary anemia, slightly improved following transfusions	Died after 2 months, 3 weeks
5	62	M	4 years, 9 months	Unsatisfactory data	Left mastoid region, cervical, epitrochlear and inguinal nodes bilaterally	Right third rib (C)	Reticulum cell lymphosarcoma	Irradiated roentgen therapy	Moderate secondary anemia; eosinophilia present	Living after 1 year
6	42	M	1 year	Tumor of left mandible 1 year before; deafness 2 months before	Mass extending above temporal region and downward to mandible, mediastinum	Left mandible (C)	Lymphosarcoma	Irradiated roentgen therapy	Blood normal	Not followed after 6 months, 3 weeks
7	30	M	2 months	Unsatisfactory data	Right cervical nodes, right tonsil, mediastinum	Left femur (C); pathologic fracture	Lymphosarcoma	Radium emanation pack, 9/6/31 to 9/14/31	Unsatisfactory data	Died after 20 days

8	9	F	3 weeks	Mass in left cheek 3 weeks before	Mass in left cheek, nodes in left submaxillary region	Left malar bone (C)	Lymphosarcoma	Irradiated roentgen therapy 6/20/27 to 5/23/28; radium emanation pack 6/14/28 to 7/2/28	Red cell count normal; moderate leukocytosis	Died after 1 year 1 month
9	24	M	1 year 9 months	Pain in lumbar region 9 months before; pain in interscapular region 3 months before; extensive herpes zoster on right shoulder girdle 1 week later; symptoms of compression of the cord 3 months later	Left cervical nodes, tonsils, inguinal nodes bilaterally	Thoracic vertebrae 1, 2, 3 (P)	Lymphosarcoma	Radium emanation pack 10/30/33; low-voltage roentgen therapy 6/4/34 to 9/3/34	Contradictory data	Died after 5 months
10	30	F	6 months	Pain in right mandible 6 months before; teeth removed at intervals before	Left cervical nodes, left axilla, left supraclavicular fossa, inguinal nodes bilaterally	Right mandible (C)	Lymphosarcoma	Radium emanation pack 2/23/34; 4/16/34 to 4/17/34	Moderate secondary anemia	Died after 2 months, 1 week
11	44	M	2 months, 3 weeks	Pain in lower part of back 2 months before; pain radiating down left leg 3 months before; rigidity of lower dorsal spine on admission	Axillae, right supraclavicular fossa, inguinal nodes bilaterally; mediastinum	Lumbar vertebra 4 (C)	Lymphosarcoma	Irradiated roentgen therapy 4/22/30 to 10/22/30	[illegible] anemia; moderate ... albuminuria	Died after 7 months
12	[illegible]	M	3 months, 3 weeks	Pain in lower part of abdomen 3 months and 3 weeks before; symptoms of compression of the cord 2 weeks before	Mass in left hypochondrium, retroperitoneal nodes, mediastinal nodes, terminal ileum, diaphragmatic pericardium, parietal pleura, epidural tissues, splenic enlargement	Lumbar vertebra 2 (C), right femur (C)	Reticulum cell lymphosarcoma	Irradiated roentgen therapy 6/21/30 to 6/24/30	Blood normal	Died after 3 weeks

TABLE 70 LYMPHOSARCOMA (*Continued*)

Case	Age	Sex	Duration of Disease Prior to Change in Bones	Symptoms Related to Changes in Bones (Before and After Roentgenographic Evidence)	Demonstrable Involvement of Viscera and Nodes	Involvement of Bones*	Microscopic Examination	Treatment of Bones	Laboratory Observations	Duration of Life Subsequent to Changes in Bones
13	24	M	6 months	Pain in left hip 3 months before	Tonsils, cervical, inguinal and axillary nodes bilaterally submaxillary region bilaterally swelling of left hip	Left femur (C) pathologic fracture	Reticulum cell lymphosarcoma	Irradiated roentgen therapy 8/20/32 to 9/[illegible]/32 total irradiation 8/22/32 (40% S.E.D †)	Moderate secondary anemia	Died after 6 weeks
14	11	M	6 months	Pain in left shoulder 6 months before; swelling of left scapula 6 months before	Swelling of supraspinous fossa, splenic enlargement pelvic nodes, mesenteric nodes, jejunum, kidneys, stomach	Left scapula (P)	Lymphosarcoma	Radium emanation pack 3/1/32 to 6/10/32	Moderate secondary anemia	Died after 5 months
15	32	F	10 months	Pain in right thigh immediately before; pain about right side of head 3 months before	Generalized lymphadenopathy; spleen and liver enlarged, retroperitoneal mass felt	Femurs (C) skull (C)	Lymphosarcoma	Irradiated roentgen therapy	Severe secondary anemia, differential count revealed preponderance of lymphocytes, moderate eosinophilia; moderate leukocytosis near end of disease	Died after 7 months
16	65	M	2 years, 8 months	Insufficient data	Cervical nodes bilaterally supraclavicular fossa, axillae, spleen, liver inguinal nodes	Pelvis (P); spine; upper end of femur (P)	Reticulum cell lymphosarcoma	Irradiated and low voltage roentgen therapy	Persistent moderate leukocytosis with an increase in lymphocytes, moderate eosinophilia	Living after 1 year
17	30	M	3 months	Pain and limping 1 month before	Left supraclavicular fossa, right cervical nodes, retroperitoneal region, left inguinal and femoral area	Pelvis (C)	Reticulum cell lymphosarcoma	Irradiated roentgen therapy	Blood normal	Living after 3 months

* C denotes osteoclastic P osteoplastic involvement.
† S.E.D indicates skin erythema dose.

secondary anemia. Transfusions temporarily improved the blood picture. The white cell count varied from that of leukopenia to that of marked leukocytosis suggesting the onset of lymphatic leukemia. In two patients the white cell count showed lymphocytes ranging from 24 to 57 per cent Ten patients were found to have from 1 to

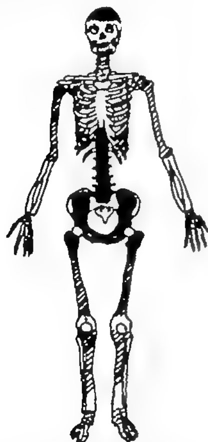


FIG. 383 Distribution of osseous lesions in lymphosarcoma with skeletal involvement. The solid black areas represent the sites most frequently involved, the checkered areas, the sites commonly involved, the diagonal lines, those invaded occasionally; the white portions, those rarely involved.

8 per cent eosinophils. A mild leukocytosis was often reduced to a normal level by irradiation. One patient's urine was examined for Bence-Jones bodies and found to be negative.

As a rule the patients were in relatively good condition until near the end of the disease.

Involvement of Bone The bones involved in lymphosarcoma were in the order of frequency the spine, pelvis, skull, femur

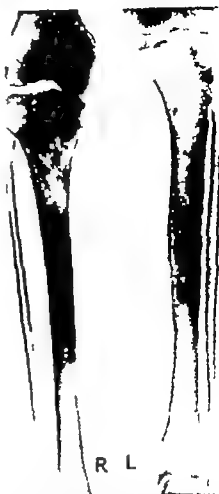


FIG. 384 Roentgenogram showing thickening of the cortex with some periosteal proliferation in the left tibia produced by lymphosarcoma Within the thickened cortex and in the upper shaft punctate areas of destruction are seen An area of rarefaction and destruction is seen in the upper shaft of the right tibia. A periosteal reaction is visible on the lateral side of the shaft.

humerus, tibia, scapula, mandible, fibula and ribs (Fig. 383) Pathologic fracture occurred five times. In one case pathologic fracture occurred in the left humerus and in both femurs. Collapse of diseased vertebrae was rare. Roentgenographically the lesions in the bones were either predominantly osteoplastic (Fig. 384) or osteolytic (Fig. 385) In the long bones the disease had no

TABLE 79 LYMPHOSARCOMA (*Continued*)

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13	24	M	6 months	Pain in left hip 3 months before	Tonsils, cervical, inguinal and axillary nodes bilaterally submaxillary region bilaterally swelling of left hip	Left femur (C) pathologic fracture	Reticulum cell lymphosarcoma	Irradiated roentgen therapy 8/30/33 to 9/8/33; total irradiation 8/22/33 (40% S.E.D.†)	Moderate secondary anemia	Died after 6 weeks
14	11	M	6 months	Pain in left shoulder 6 months before swelling of left scapula 6 months before	Swelling of supraspinous fossa, spleen enlargement, pelvic nodes, mesenteric nodes, jejunum, kidneys, stomach	Left scapula (P)	Lymphosarcoma	Radium emanation pack 5/1/32 to 6/10/32	Moderate secondary anemia	Died after 5 months
15	32	F	10 months	Pain in right thigh immediately before; pain about right side of head 3 months before	Generalized lymphadenopathy; spleen and liver enlarged retroperitoneal mass felt	Femora (C); skull (C)	Lymphosarcoma	Irradiated roentgen therapy	Severe secondary anemia, differential count revealed preponderance of lymphocytes moderate eosinophilia, moderate leukocytosis near end of disease	Died after 7 months
16	65	M	2 years, 6 months	Insufficient data	Cervical nodes bilaterally supraclavicular fossa, axillae, spleen liver inguinal nodes	Pelvis (P) spine; upper end of femur (P)	Reticulum cell lymphosarcoma	Irradiated and low-voltage roentgen therapy	Persistent moderate leukocytosis with an increase in lymphocytes; moderate eosinophilia	Living after 1 year
17	30	M	8 months	Pain and limping 1 month before	Left supraclavicular fossa, right cervical nodes, retroperitoneal region, left inguinal and femoral area	Pelvis (C)	Reticulum cell lymphosarcoma	Irradiated roentgen therapy	Blood normal	Living after 3 months

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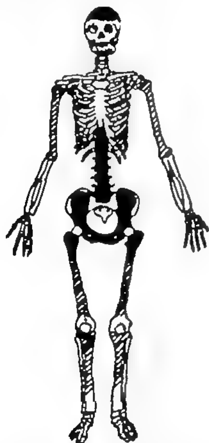


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FIG. 384 Roentgenogram showing thickening of the cortex with some periosteal proliferation in the left tibia produced by lymphosarcoma. Within the thickened cortex and in the upper shaft punctate areas of destruction are seen An area of rarefaction and destruction is seen in the upper shaft of the right tibia. A periosteal reaction is visible on the lateral side of the shaft.

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TABLE 79 LYMPHOSARCOMA (*Continued*)

Case	Age	Sex	Duration of Disease Prior to Change in Bones	Symptoms Related to Changes in Bones (Before and After Roentgenographic Evidence)	Demonstrable Involvement of Viscera and Nodes	Involvement of Bones*	Microscopic Examination	Treatment of Bones	Laboratory Observations	Duration of Life Subsequent to Changes in Bones
13	31	M	6 months	Pain in left hip 2 months before	Tonsils, cervical, inguinal and axillary nodes bilaterally, submaxillary region bilaterally swelling of left hip	Left femur (C); pathologic fracture	Reticulum cell lymphosarcoma	Irradiated roentgen therapy 8/20/33 to 9/4/33; total irradiation 8/27/33 (40%, 6 L.D †)	Moderate secondary anemia	Died after 6 weeks
14	11	M	6 months	Pain in left shoulder 6 months before swelling of left scapula 6 months before	Swelling of supraclavicular fossa, spleen enlargement, pelvic nodes, mesenteric nodes, jejunum, kidneys, stomach	Left scapula (P)	Lymphosarcoma	Radium emanation pack 8/1/33 to 8/10/33	Moderate secondary anemia	Died after 5 months
15	22	F	10 months	Pain in right thigh immediately before; pain about right side of head 4 months before	Generalized lymphadenopathy; spleen and liver enlarged; retroperitoneal mass left	Femurs (C); skull (C)	Lymphosarcoma	Irradiated roentgen therapy	Severe secondary anemia; differential count revealed preponderance of lymphocytes, moderate eosinophilia, moderate leukocytosis near end of disease	Died after 7 months
16	53	M	2 years, 2 months	Insufficient data	Cervical nodes bilaterally, supraclavicular fossa, axillae, spleen, liver inguinal nodes	Pelvis (P); spine; upper end of femur (P)	Reticulum cell lymphosarcoma	Irradiated and low-voltage roentgen therapy	Persistent moderate leukocytosis with an increase in lymphocytes; moderate eosinophilia	Living after 1 year
17	[illegible]	M	5 months	Pain and limping 1 month before	Left supraclavicular fossa, right cervical nodes, retroperitoneal region, left inguinal and femoral area	Pelvis (C)	Reticulum cell lymphosarcoma	Irradiated roentgen therapy	Blood normal	Living after 3 months

* C denotes osteoclastic, P osteoplastic involvement.
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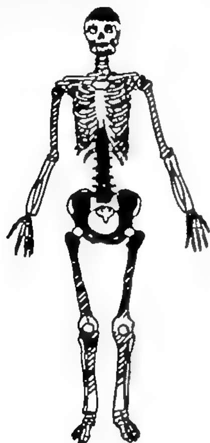


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TABLE 70 LYMPHOSARCOMA (*Continued*)

Case	Age	Sex	Duration of Disease Prior to Changes in Bones	Symptoms Related to Changes in Bones (Before and After Roentgenographic Evidence)	Demonstrable Involvement of Viscera and Nodes	Involvement of Bones*	Microscopic Examination	Treatment of Bones	Laboratory Observations	Duration of Life Subsequent to Changes in Bones
13	21	M	6 months	Pain in left hip 3 months before	Tonsils, cervical, inguinal and axillary nodes bilaterally, subaxillary region bilaterally swelling of left hip	Left femur (C); pathologic fracture	Reticulum cell lymphosarcoma	Irradiated roentgen therapy 8/20/33 to 9/6/33; total irradiation 8/22/33 (40% S E D †)	Moderate secondary anemia	Died after 6 weeks
14	11	M	6 months	Pain in left shoulder 6 months before; swelling of left scapula 6 months before	Swelling of supraspinous fossa, spleen enlargement pelvic nodes, mesenteric nodes, jejunum, kidneys, stomach	Left scapula (P)	Lymphosarcoma	Radium emanation pack 5/1/33 to 6/10/33	Moderate secondary anemia	Died after 5 months
15	32	F	10 months	Pain in right thigh immediately before; pain about right side of head 3 months before	Generalized lymphadenopathy; spleen and liver enlarged; retroperitoneal mass left	Femurs (C); skull (C)	Lymphosarcoma	Irradiated roentgen therapy	Severe secondary anemia; diff. medial count revealed preponderance of lymphocytes; moderate eosinophilia moderate leukocytosis near end of disease	Died after 7 months
16	65	M	2 years, 8 months	Insufficient data	Cervical nodes bilaterally supraclavicular fossa, axillae, spleen, liver inguinal nodes	Pelvis (P); spine; upper end of femur (P)	Reticulum cell lymphosarcoma	Irradiated and low-voltage roentgen therapy	Persistent moderate leukocytosis with an increase in lymphocytes; moderate eosinophilia	Living after 1 year
17	39	M	8 months	Pain and limping 1 month before	Left supraclavicular fossa, right cervical nodes, retroperitoneal region, left inguinal and femoral area	Pelvis (C)	Reticulum cell lymphosarcoma	Irradiated roentgen therapy	Blood normal	Living after 3 months

* C denotes osteoclastic P osteoplastic involvement.
† S.E.D indicates skin erythema dose.

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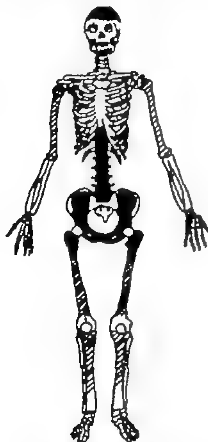


Fig. 383. Distribution of osseous lesions in lymphosarcoma with skeletal involvement. The solid black areas represent the sites most frequently involved, the checkered areas, the sites commonly involved, the diagonal lines, those invaded occasionally the white portions, those rarely involved.

As a rule the patients were in relatively good condition until near the end of the disease.

Involvement of Bone The bones involved in lymphosarcoma were in the order of frequency the spine pelvis, skull femur humerus, tibia, scapula, mandible fibula and ribs (Fig 383) Pathologic fracture occurred five times. In one case pathologic fracture occurred in the left humerus and in both femurs. Collapse of diseased vertebrae was rare. Roentgenographically the lesions in the bones were either predominantly osteoplastic (Fig. 384) or osteolytic (Fig. 385) In the long bones the disease had no



Fig. 384. Roentgenogram showing thickening of the cortex with some periosteal proliferation in the left tibia produced by lymphosarcoma. Within the thickened cortex and in the upper shaft punctate areas of destruction are seen. An area of rarefaction and destruction is seen in the upper shaft of the right tibia. A periosteal reaction is visible on the lateral side of the shaft.

predilection for the part containing marrow but infiltrated the bones extensively As the disease progressed, the entire bone was frequently involved. In general, the osteolytic

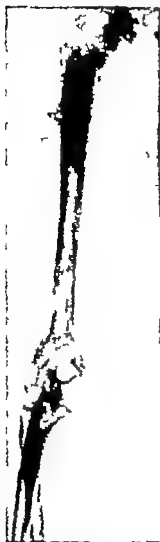


FIG. 385. Diffuse involvement of the humerus in lymphosarcoma. There is marked destruction with little or no formation of new bone. A pathologic fracture is seen at the upper end of the shaft.

changes were seen more frequently Roentgenograms of the skull showed a predominant osteoclastic reaction (Fig 386) Small miliary or larger single punched-out areas of destruction were seen. The areas of destruction were rarely surrounded by increased bone density The vertebrae showed sclerosis with some destruction of bone, occasionally with partial collapse. A periosteal reaction about the diseased vertebrae was not seen.

The pelvis, especially the ilium was frequently involved by areas of rarefaction, often small and punched-out in appearance. The sacrum and last lumbar vertebra showed similar changes. In one instance the pubis showed marked destruction with trabeculae not unlike a giant-cell tumor An osteolytic process predominated in all the pelvic lesions.

Pathology A diseased gland was available for microscopic examination in all cases and autopsies were performed on three patients.

A mass of tumor found in a femur removed at autopsy surrounded the lower end of the bone completely and involved the periosteum, forming a cuff 5 cm. long and 1.5 cm. thick. The bony cortex was eroded by the tumor The microscopic study (Fig 387) showed destruction of the bone by the tumor with no evidence of the formation of new bone. The tumor infiltrated through the haversian canals and extended beneath the periosteum. A mass of nodes was also found closely attached to the bone in the region of the fifth lumbar vertebra and in the roentgenogram the vertebra showed involvement. The invasion of the bone was by direct extension. In one case the left scapula was removed at autopsy The suprascapular fossa was found filled with rubbery opaque tumor tissue about 4 mm. thick, extending from the acromion process across the supraclavicular fossa to the vertebral border and infiltrating the underlying bones. Visceral lesions were found in all the cases examined at necropsy and the bones were invaded by direct extension of the disease.

The microscopic appearance of the lymph nodes removed for biopsy was characteristic of lymphosarcoma, a diffuse growth of lymphoid cells lying in reticular tissue. The general structure of the nodes was obliterated. The individual cells varied in

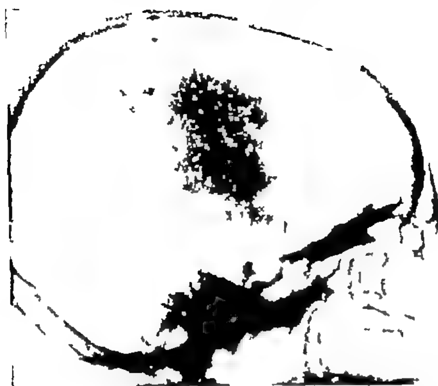


FIG. 386 Roentgenogram of the skull in a case of lymphosarcoma, showing small, multiple, punched-out areas of destruction.



FIG. 387 Microphotograph of lymphosarcoma involving the bone. The bone shows infiltration by the tumor There is no evidence of osseous regeneration.

TABLE 80 DATA ON SEVEN PATIENTS WITH CHANGES OF THE BONES ASSOCIATED WITH LEUKEMIA

Case Age Years Sex	Duration of Disease Prior to Changes of the Bones	Viscera and Nodes Demonstrably Involved	Bones Involved*	Treatment of Bones	Laboratory Findings†	Duration of Life Following Changes of the Bones
1 M N 3 F	2 months	Submaxillary axillary and inguinal nodes tonsils liver spleen	Left first metacarpal (C) left ilium (P and C)	8/12/26 to 8/27/26, high-voltage roentgen therapy	7/20/26 Hgb 20 per cent R B C 1 100,000; W.B C., 8,030 P 4; S. L. 94 My 2 Following transfusion and roentgen therapy 8/17/26 Hgb 40 per cent; R B C 4,300,000; W B C 12,400 P 47; S L. 18; L.L., 29 My 6	Dead after 2 months
2 C C 64 F	1 year 4 months	Tonsils spleen cervical and bilateral axillary and inguinal nodes	Skull (P)(C?)	2/7/30 to 3/14/31 high-voltage roentgen therapy	6/ 7/30 Hgb 90 per cent R B C 4,000,000 W.B C 10,300 P 28; S L., 50 L.L 10; My 2 1/12/31 Hgb., 75 per cent; R B C., 3,700,000; W B C., 6,900; P 39; S L. 45; L.L., 7 2/21/31 Hgb 55 per cent R B C., 2,900,000 W B C., 1,600; P., 57; S.L., 18; L L 16 T 3 My 6 Following transfusion 4/16/31 Hgb 70 per cent R B C 3,300,000 W B C 3,700; P 47; S L. 41; L L 9 T 3 7/20/31 Hgb 75 per cent R B C., 3,700,000; W B C., 4,000; P 35; S.L., 57 L L., 3 + T 3; E 3, Wassermann test, negative	Dead after 9 months 2 weeks
3 F H 40 F	1 year 4 months	Spleen, bilateral cervical, supraclavicular axillary and inguinal nodes	Pelvis (C) left femur (C)	Much radium and roentgen therapy	12/27/29 Hgb 60 per cent R B C 3,300,000; W.B C 25,600; P 48; S L., 48, L L., 7 My 2 3/21/24 Hgb 50 per cent R B C 4,200,000 W B C 9 400; P 73 S L 2, L.L. 25 4/10/24 Hgb 70 per cent; R B C 3,800,000 W B C., 4,600; P 53 S L. 48 9/24/24 Hgb. 85 per cent R B C 2,700,000; W B C. 17,500; P 64; S L., 14; L L., 19 2/ 2/23 Hgb 70 per cent R B C 4,800,000 W B C., 14,400; P 30 S.L., 66; L L., 2 My 2 9/ 3/23 Hgb 75 per cent; R B C 3,000,000; W B C 10,300; P 58; S L. 38 T ., 4, My., 2 10/ 4/26 Hgb 75 per cent R B C 3,600,000; W B C., 3,000 P 65 S L 16; L L., 9; T 6, My 4 11/ 4/26 Hgb 60 per cent., R.B C 3,300,000; W B.C., 2,400; P 60; S.L., 24; L L 9 T 7	Dead after 2 years 9 months
4 F C 32 F	1 year	Submaxillary and bilateral cervical axillary and inguinal nodes spleen and submental region	Left and right femur (P)	11/23/31 Heublein unit therapy 13% L D 6/9/32, Heublein unit therapy 31% L D	8/ 1/31 Hgb 80 per cent; R.B C 4,000,000; W B C. 12,100; P 23; S L., 71 L L 3; Tr 3 8/21/31 Hgb 60 per cent R B C 3,000,000; W B C. 3,400; P., 32 S.L., 55; L L. 3; T 11 12/ 2/31 Hgb 60 per cent, R B C 4,000,000; W B C., 4,700; P 49; S L., 42 L L., 5 Tr 4 6/ 9/32 Hgb 80 per cent; R B C 3,900,000; W.B C 2,000; P 36; S L., 43; L L 10; T 3; E 8; Platelets, 290,000 9/23/32 W B C 2,900; P 47; S L. 25 L.L., 4 T 1 E., 3	Living after 2 years
5 R H 53 M	3 years, 8 months	Cervical and bilateral mediastinal, retroperitoneal, inguinal and femoral nodes spleen	Right humerus (C)	11/12/31 Heublein unit therapy 25% L D 1/15/32, Heublein unit therapy 25% E D	11/12/31 B.M R. +60+80; Hgb 73 per cent; R B C 3,800,000; W B C., 6,000 P , 43 S L 22; L.L., 33 1/ 7/32 Hgb 75 per cent; R B C 3,600,000; W B C., 2,400; P 56 S.L., 30; L L., 12 6/ 9/32 Hgb 65 per cent; R B C 3,400,000; W B C 8,200 P 86 S L., 4; L.L., 4 T 3 My 3 8/1 /32 W B C., 3,000; P 35 S L 38 L.L 5 T 3 My 2 8/18/32 B J B., none	Died after 4 months (autopsy: pseudoleukemia)
6 A O 72 M	2 years, 4 months	Spleen cervical and bilateral axillary and inguinal nodes tonsils	Eleventh thoracic vertebra (C)	2/20/33, high voltage roentgen therapy	2/ 2/30 Hgb 93 per cent R B C 4,000,000; W B C., 43,800; P 17; S L., 72; L L 18; Tr 1 2/ 3/31 Hgb 80 per cent; R B C 4 100,000; W B C., 11,700; P 48 S L., 44; L L 9; T 2 12/10/31 Hgb 80 per cent; R B C., 3,900,000; W B C 7 400 P 40 S L., 44; L L. 7; T 3; E 2 2/17/33 Hgb 75 per cent R.B C., 3,600,000; W.B C 11,900; P 39; S L., 43; L.L., 7; T 2 E 4	Living after 3 months
7 H M 30 F	8 months	Cervical and bilateral inguinal nodes spleen, liver	Right humerus (C); right femur (C) left femur (C)	No treatment of bones	8/19/32 Hgb 100 per cent (Dare); R B C 6,000,000; W.B C., 5,000; P 34 S L 3 8 B. 3 5; My 33 Mybl 11.5, E My 3 8/26/32. W B C 24,000; P 64; S L., 14, My , 16 5; E My., 3 5; B My 4 5 8/31/32: W.B C 20,000; P., 75 5; S L 3; E.My 1; B 1 5 My 17	Living after 9 months

* Osteoclastic is indicated by C and osteoplastic by P

† Hemoglobin is indicated by Hgb red blood cells, by R.B C white blood cells, by W.B C polymorphonuclears, by P small lymphocytes, by S.L. large lymphocytes, by L.L. myelocytes, by My transitionals, by Tr basal metabolic rate, by B.M R. eosinophils, by E. myeloblasts, by Mybl. basophils, by B ; erythema doses, by E.D Bence-Jones bodies, by B J B

size. Multinucleated cells were not observed (Fig 387)

As in Hodgkin's disease, the treatment of lymphosarcoma is by irradiation The lesions of bone may be treated either by single large suberythema doses or by fractional doses with high voltage roentgen rays. Relief from pain is usually prompt. Reparative changes in the bones may be observed after treatment. In the terminal stages of the disease, routine irradiation of all the bones is not attempted This conservative attitude is taken because of the severe anemia which exists in the late stages of the disease.

The palliative forms of therapy which apply to Hodgkin's disease such as oil soluble nickel, nitrogen mustard and radioactive calcium, are less effective in lymphosarcoma.

LYMPHATIC LEUKEMIA

Bone changes associated with lymphatic or myeloid leukemia are relatively rare The osseous manifestations often appear late in the disease and if the prior clinical course has been typical of leukemia, with characteristic changes in the peripheral blood, the diagnosis is not subject to dispute. However when bone manifestations are prominent and appear early the entity of leukemia is apt to be confused with so-called myelogenous myeloma or chloroma

In adults, lymphatic leukemia is associated with osseous changes more often than the myelogenous variety In 86 patients with lymphoid leukemia, Craver and Copeland found 6 patients (7 per cent) in whom bone changes were demonstrable in the roentgenogram (Table 80)

The duration of the disease before and following demonstrable changes in the bones varies from several months to over three years. Apparently there is no correlation between the early development of changes in the bones and the duration of life after such changes occur

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FIG. 388 (No. 49350) Roentgenogram showing bone involvement in lymphoid leukemia Longitudinal areas of rarefaction are seen in the long bones of the lower extremities. The patient was a girl aged 4½ years, whose first complaint was pain in the right hip accompanied by limping This was followed by polyarthritis with purpuric spots. The white count was 8 000 with 80 per cent lymphocytes.

Such regions are usually tender to pressure. Moderate enlargement of the spleen, enlargement of superficial and deep lymph nodes, cachexia, anemia, and a relative increase in the lymphocytes of the blood are characteristic of the clinical course In the cases studied by Craver and Copeland at Memorial Hospital there were six adults and one infant. The total white count remains low in these cases, varying from five to twelve thousand. In two cases (Table

TABLE 80. DATA ON SEVEN PATIENTS WITH CHANGES OF THE BONES ASSOCIATED WITH LEUKEMIA

Case; Age Years; Sex	Duration of Disease Prior to Changes of the Bones	Viscera and Nodes Demonstrably Involved	Bones Involved	Treatment to Bones	Laboratory Findings †	Duration of Life Following Changes of the Bones
1 M N 7 F	2 months	Submaxillary axillary and inguinal nodes tonsils liver spleen	Left first metacarpal (C) left ulna (P and C)	8/12/26 to 8/27/26, high-voltage roentgen therapy	7/26/26 Hgb 20 per cent R B C 1,100,000 W B C 8,030 P 4; S L., 94; My 2 Following transfusion and roentgen therapy 8/17/26 Hgb 80 per cent R B C 4,200,000 W B C 12,400; P 47 S L 16; L.L., 29; My 8	Dead after 3 months
2 C C 65 F	1 year 3 months	Tonsils, spleen cervical and bilateral axillary and inguinal nodes	Skull (P)(C*)	2/7/30 to 3/14/31 high-voltage roentgen therapy	6/ 7/30 Hgb 90 per cent; R B C., 4,000,000 W B C., 10,300 P 24 S L., 59; L L 10 My 3 1/12/31 Hgb., 75 per cent R B C., 2,700,000; W.B C 6,900; P., 33; S L 53 L.L., 7 2/21/31 Hgb., 85 per cent R B C. 3,900,000; W.B C., 1,800; P 57; S L., 16; L.L 18; T 3; My 6 Following transfusion 4/16/31 Hgb., 70 per cent; R B C 3,300,000; W.B C 3,700; P 47; S L. 41; L L 9 T 3 7/30/31 Hgb 73 per cent R B C. 3,700,000; W.B C., 4,000; P 53 S L., 37 L L., 3 + T 3 E. 3. Wassermann test, negative	Dead after 9 months, 2 weeks
3 F H 40 F	1 year 3 months	Spleen, bilateral cervical infraclavicular axillary and inguinal nodes	Pelvis (C) left femur (C)	Much radium and roentgen therapy	12/27/23 Hgb 60 per cent; R B C 3,300,000; W.B C. 38,000; P 48; S L 45 L L., 7; My., 3 3/31/24 Hgb 80 per cent, R B C. 4,300,000; W B C., 9,900 P 72 S L 2; L L 28 4/10/24 Hgb 70 per cent R B C 3,900,000 W B C. 4,000 P 55; S L., 45 9/25/24 Hgb 38 per cent; R B C. 2,700,000 W B C 17,300; P 84; S L., 14 L.L. 18 3/ 3/25 Hgb 70 per cent R.B C. 4,500,000 W.B C. 14,800 P., 30 S L., 66; L L 2; My., 2 9/ 3/25 Hgb 78 per cent, R B C., 3,600,000 W.B C 10,300 P 58; S L 36 T 4, My., 2 10/ 4/26 Hgb 78 per cent; R B C 3,600,000; W B C., 3,000; P 65; S L 16; L.L., 9; T 6; My 4 11/ 4/26 Hgb. 60 per cent; R B C 2,400,000; W B C., 2,400 P 60; S L., 24; L L 9 T 7	Dead after 2 years 9 months
4 F C 32 F	1 year	Submaxillary and bilateral cervical, axillary and inguinal nodes, spleen and subcarinal region	Left and right femur (P)	11/23/31 Heublein unit therapy 13% E D 8/9/32, Heublein unit therapy 24% E D	8/ 1/31 Hgb. 80 per cent R.B C 4,000,000 W B C 12,100; P 23; S.L., 71 L L., 3; T 3 8/21/31 Hgb., 80 per cent; R B C 3,000,000; W B C. 4,400; P., 25; S L., 55; L L., 2; T 11 12/ 2/31 Hgb 80 per cent; R B C., 4,000,000; W B C., 4,700 P., 49 S.L 42; L L 5 T 4 8/ 9/32 Hgb 80 per cent R B C., 3,900,000 W.B C 3,000; P 36 S L., 43 L.L., 10; T 3; E 8 Platelets, 290,000 9/22/32 W.B C. 3,400 P 47; S L 23 L L 4 T 1 E., 2	Living after 2 years
5 R H 33 M	3 years, 5 months	Cervical and bilateral mediastinal, retroperitoneal, inguinal and femoral nodes spleen	Right humerus (C)	11/13/31 Heublein unit therapy 25% E D 1/16/32, Heublein unit therapy 25% E D	11/13/31 B M R 40-60 Hgb 73 per cent; R B C., 3,800,000; W.B C. 6,000 P., 43 S L 22; L.L., 33 1/ 7/32 Hgb., 75 per cent R B C 3,800,000; W B C 5,400; P 56; S.L 20; L L., 12 4/ 4/32 Hgb 65 per cent; R B C., 3,400,000 W B C., 6,300 P 85 S.L 5 L L 4; T 3; My 3 5/17/32 W B C., 3,600 P 55 S L 34; L.L. 5 T 3 My., 3 5/18/32 B J B none	Died at 4 months (autopsy: pseudoleukemia)
6 A G 73 M	2 years, 4 months	Spleen; cervical and bilateral axillary and inguinal nodes; tonsils	Eleventh thoracic vertebra (C)	3/20/33, high voltage roentgen therapy	2/ 2/30 Hgb 85 per cent, R B C 4,800,000 W B C., 43,200; P 17 S L. 72; L L 15 T 1 2/ 3/31 Hgb 80 per cent R B C 4,100,000 W B C., 11,700 P., 48 S L. 44 L.L., 9 T 2 12/10/31 Hgb 80 per cent R B C 3,900,000; W B C., 7,400 P 49; S L., 44 L L., 7; T 3; E 2 2/17/33 Hgb. 75 per cent; R B C., 3,600,000 W B C 11,800; P 30 S L., 48; L L. 7; T 2 E 4	Living after 3 months
7 H M 59 F	8 months	Cervical and bilateral inguinal nodes; spleen liver	Right humerus (C) right femur (C) left femur (C)	No treatment to bones	5/19/33 Hgb 100 per cent (Dare); R B C., 6,000,000 W B C 5,300 P 54; S L., 2 S B [illegible]; My 28, Mybl 11.5; E.My 3 5/26/33 W B C., 34,000; P 61; S L., 14; My 10.5; T My 3.5; B My 4.3 5/31/33 W B C 30,300; P 73.5; S L 4; E.My 1; B 1.5 My 17	Living after 9 months

* Osteoclastic is indicated by C and osteoplastic by P

† Hemoglobin is indicated by Hgb. red blood cells, by R.B C white blood cells, by W.B C polymorphonuclears, by P, small lymphocytes, by S.L. large lymphocytes, by L.L. myelocytes, by My transitionals, by T basal metabolic rate, by B.M R. eosinophils, by E. myeloblasts, by Mybl. basophils, by B erythema doses, by E.D Bence-Jones bodies, by B-J B

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FIG. 388 (No. 49350) Roentgenogram showing bone involvement in lymphoid leukemia. Longitudinal areas of rarefaction are seen in the long bones of the lower extremities. The patient was a girl aged 4½ years, whose first complaint was pain in the right hip accompanied by limping This was followed by polyarthritis with purpuric spots. The white count was 8 000 with 80 per cent lymphocytes.

Such regions are usually tender to pressure. Moderate enlargement of the spleen, enlargement of superficial and deep lymph nodes, cachexia, anemia, and a relative increase in the lymphocytes of the blood are characteristic of the clinical course. In the cases studied by Craver and Copeland at Memorial Hospital there were six adults and one infant. The total white count remains low in these cases, varying from five to twelve thousand. In two cases (Table



Fig 389 (No 49350) Roentgenogram showing the lateral view of the lower and upper extremities from the case shown in Figure 388. Note the overlying periosteal reaction in the tibia.

80) counts of 38 600 and 49,200 were observed.

The long bones, particularly the femur and humerus, are more frequently affected in lymphatic leukemia than the pelvis, skull or vertebrae. In the roentgenogram longitudinal areas of rarefaction in the long bones overlaid by the delicate longitudinal periosteal reaction is a characteristic finding (Figs. 388 and 389) Small, triangular areas of subcortical rarefaction just behind the epiphyseal line are also characteristic manifestations. The involvement in a single long bone at times resembles the changes seen early in Ewing s sarcoma but the involvement of several bones and longitudinal areas of bone destruction in the marrow cavity with intervening normal bone between the periosteal and medullary zones are distinguishing features. In the skull, small osteoporotic changes with a neighboring periosteal elevation or thinning of the inner and outer tables are seen (Fig 390)

At autopsy the bone involvement in lymphatic leukemia shows hyperplastic nodules *in the bone marrow which* are at first discrete, but which gradually coalesce. The disease extends throughout the marrow attacks the spongy trabeculae and invades the haversian spaces. Microscopically the diseased tissue resembles lymphosarcoma or Ewing s sarcoma of bone. The involvement of the liver and spleen in leukemia, however is diagnostic, when taken in conjunction with the altered leucocyte count.

MYELOID LEUKEMIA

If cases of chloroma are excluded from those of myeloid leukemia, bone involvement is exceptional in those past infancy Of 82 patients with myeloid leukemia studied by Craver and Copeland at Memorial Hospital, only one, a woman aged 59 showed bone involvement. Leukemic manifestations in the blood were discovered eight months prior to the changes in the bone and the patient was reported living nine months after the appearance of the skeletal changes. The white-cell count was not high and varied from 5 000 to 34,000 Myelocytes were a constant feature. The bone changes in this case were a combination of osteoporosis and osteosclerosis. The most marked changes were in the upper portion of both femurs, where multiple punched out areas were found in the roentgenogram.

The majority of cases of leukemia in infants and children are myelogenous in type. The former opinion that lymphogenous forms predominated was due to the difficulty in differentiating the myeloblasts from the lymphoblasts. In children with acute myelogenous leukemia, there is often a subleukemic count, with blast forms predominating in the differential smear With either the leukemic or subleukemic blood picture, it is not rare to have bone pains which will prevent the child from walking. In such cases with pain referred



FIG. 390 (No 49350) Roentgenogram of the skull from the case of leukemia shown in Figure 388. There are minute areas of destruction in the calvarium with thinning of the tables and a faint periosteal reaction.

to the limbs, a diagnosis of rheumatic fever may be suggested. The differential count and bone marrow smear however are diagnostic. In such cases, roentgenograms of the long bones may reveal triangular defects in the cancellous substance just behind the epiphyseal line. Bone involvement with protuberant masses in the region of the orbit may be a presenting feature. This is also found in cases of neuroblastoma of the adrenal with bone metastases, and in forms of leukemia, known as chloroma.

In both lymphatic and myelogenous leukemia, palliative irradiation is a valuable form of treatment, unless there is a subleukemic count and a severe anemia. Then multiple transfusions must be given and



FIG. 391 Bone involvement in the humerus in myelogenous leukemia in a child.

nitrogen mustard may be tried. The oil soluble metals, copper in myelogenous leukemia, and nickel in lymphatic leukemia urethane or aminopterin may produce remissions. The lowering of the platelet count, with a hemorrhagic tendency is often the cause of exodus in these cases.

infiltration of muscles and tendinous attachments by way of the bone. One of our cases was a male aged 17 years with involvement of the humerus and skull. The white blood count was 30 000 with myeloblasts and other premature forms in the stained smears. A pathologic fracture ultimately occurred in the humerus. The roentgenogram (Fig 393) showed marked involvement at the level of the deltoid tubercle with periosteal lifting and right angle new-bone formation. The cortex showed osteoporosis and some definitely punched-out areas. The skull was invaded, causing destruction of bone and pressure on the orbital structures with exophthalmos. A second patient was a white male, 17 years of age, who had swelling of all his joints for two months. There was warmth but no redness. One month later fixation of the mandibular joints occurred. Several bad teeth were extracted followed by severe hemorrhage Following this, tumors developed over the head and behind the eyes, causing both eyes to protrude There was marked edema of both eyelids. Examination revealed marked exophthalmos with

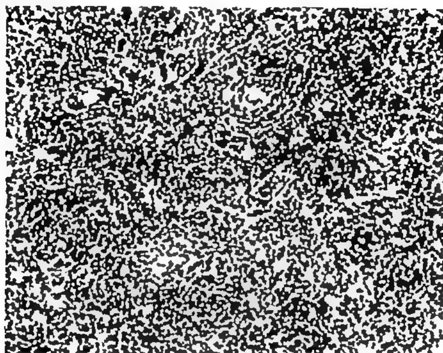


Fig 392. Photomicrograph of myeloblastic leukemia involving bone.

CHLOROMA

The occurrence of greenish tumors of the skull vertebrae, ribs and other organs was first given the name of chloroma by King in 1853 and in 1885 von Recklinghausen established its probable relation to leukemia. More recently detailed blood studies have completed the parallel with leukemia by showing the existence of both a myelogenous and a lymphatic type of chloroma. The disease occurs usually in children approaching puberty and terminates fatally within an average period of five months. Adults are occasionally affected. The tumors appear chiefly in the skull and cause symptoms referable to the eye, ear nose and throat. Often there are associated foci in the sternum, spine, ribs, pelvis and long bones. Ewing notes a special tendency to

edema of lids and swelling about the jaws and face. Enlargement of lymph nodes, liver and spleen was found. Roentgen examination revealed areas of bone destruction in the cranial bones about the orbit rim of granular cytoplasm. The blood calcium was 11.5 mg per cent, the urine negative for Bence-Jones bodies. A lymph node removed for examination was definitely green in color Microscopic examination



FIG. 393. Chloroma of the humerus with pathologic fracture Diffuse osteoporosis of the cortex and periosteal proliferation are striking features.

and areas of rarefaction in the long bones of the extremities. The largest area was in the lower end of the left humerus. Laboratory examinations showed a red blood cell count of 3,350,000 The hemoglobin was 48 per cent the white blood cells 24,200 with 83 per cent myeloblasts. These were unusually large with a big nucleus and a revealed a typical picture of chloroma. There was an increase in the stroma of the gland and a crowding of large atypical monocytes everywhere (Fig. 394) The nuclei of these cells showed numerous mitotic figures and were often hyperchromatic. The patient was given deep roentgen therapy Three hundred and

fifty roentgens were given over the cervical, inguinal and splenic areas. Similar irradiation was given to the head, shoulders and region of the elbows. There was marked improvement during the treatment but within a few days the white count dropped

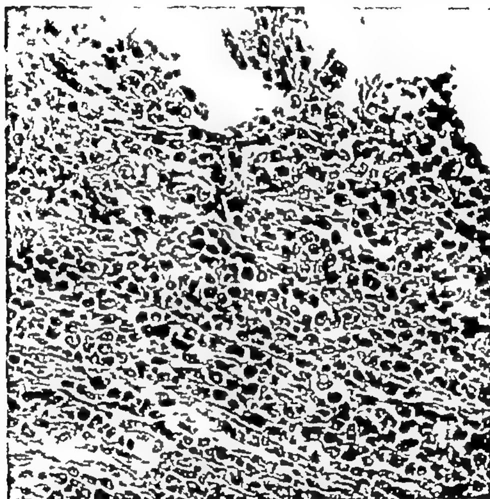


FIG. 394. Microphotograph of chloroma. Note atypical cell forms, myeloblasts and premature polymorphs.

to 1500 This was raised to 3,000 by repeated small transfusions. The patient developed gangrene in the region of the left lower mandible involving the gingivobuccal fold and died ten days later

Although lymphoid varieties have been described, we have not seen them. We have however observed bone involvement similar to chloroma with primitive-cell and monocytic leukemia. The disease described as chloroma is apparently a form of myeloid leukemia in which bone manifestations are the prominent feature. The only distinguishing feature from the standpoint of pathology is the green color observed in the tumor tissue in the gross. The myeloid form of chloroma may be looked upon as atypical myeloid leukemia with a tendency to affect the bones in young individuals. This corresponds to the atypical forms of lymphoid leukemia with characteristic bone involvement which is seen in infants.

The lesions in chloroma are radiosensitive and deep roentgen therapy supplies a valuable palliative treatment. The dosage however must be small and carefully administered since both the white blood cell count



FIG. 395 Roentgenograms depicting bone changes in a woman of 34 years with Mediterranean anemia. The accentuated trabeculations are characteristic. (Walsh, W B Bull. Georgetown Univ Med. Center 1: 70)

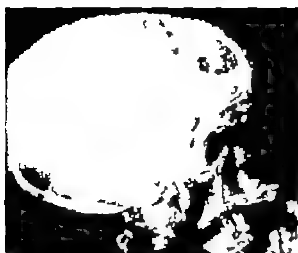


FIG. 396 (No 49610) Roentgenogram of the skull in a case of erythroblastosis. Note the thickened skull in the frontal and occipital regions.

and the red-blood-cell count may rapidly diminish under irradiation.

ERYTHROBLASTIC ANEMIA

Characteristic bone changes are observed in young children with erythroblastic anemia. This disease which has a definite racial and familial tendency is characterized by nucleated red blood cells in the peripheral circulation, enlargement of the liver and spleen and a fatal termination. Cooley first described this condition in 1925 distinguishing it from the group of anemias, described by Von Jaksch. In the last ten years numerous cases have been reported and Strong in 1935 was able to collect a total of 59 cases. Practically all patients affected are from Mediterranean countries including Italians, Greeks and Armenians. In many of the cases, more than one member of the family was affected. Males and females are both susceptible. With few exceptions the disease occurs in the first two years of life. The earliest case reported was three months and the oldest ten years. The onset of the disease is characterized by pallor weakness and listlessness The abdomen is usually enlarged with palpable liver and spleen and the face has a Mongoloid appearance. This is produced by enlargement of the skull and malar bones.

Roentgenograms of the skull early in the disease show increased porosity Later the skull becomes thickened and fine cross striations appear in the diploe accompanied by radiating spicules projecting at right angles from the outer table (Fig. 396.) The malar bones are enlarged, the long bones show increased porosity and characteristic transverse trabeculations which are most prominent in the small bones of the hand. Thinning of the cortex and small, rounded areas of destruction may appear The bone changes resemble those occasionally seen in hemolytic jaundice and sickle-cell anemia, but are more prominent. Whipple believes that they are due to metabolic changes.

The blood picture is characterized by anemia ranging from 1,000 000 to 4,000 000 red blood cells platelets appear in normal numbers. There is frequently a leucocytosis of 20,000 or more but a relatively normal differential count. Normoblasts are found and may number as many as five per high-power field. Degenerated erythroblasts and erythrocytes are common. The pathologic changes are most marked in the bone marrow spleen and liver In the bone, the cortex is thin and the red marrow hyperplastic, the spleen is enlarged and the capsule thickened. Erythroblastic elements similar to those found in the bone marrow appear in great numbers in the splenic pulp The liver shows hemopoiesis and deposits of iron pigment in the Kupffer and liver cells.

While the majority of individuals afflicted with Mediterranean anemia die in childhood or infancy some of these patients may survive and reach adulthood. The authors have observed two such cases and in all of them the bone changes have been marked, with multiple cystic areas which tend to become confluent and lead to pathologic fractures. Figure 395

There is no specific therapy Small transfusions repeated at frequent intervals give

temporary relief The spleen may be removed if its enlargement causes great discomfort. The patients eventually die.

SICKLE-CELL ANEMIA

This hereditary familial disease is peculiar to Negroes. It is characterized by the presence of sickle shaped red corpuscles which may be present in the fresh blood but generally appear on standing These patients suffer from severe anemia, leg ulcers, rheumatic pains and attacks of excessive blood destruction and active blood formation. Anemia, jaundice and weakness are common. Bone deformities may be a prominent feature of the disease These include kyphosis, scoliosis, saber shin, tower shaped skull and rarefied spongy bone within a thin cortex which is nearly radiotranslucent. Radiating spicules of the outer and inner tables of the skull may resemble in the roentgenogram the picture seen in Cooley's anemia. The tower skull seen in sickle-cell anemia may occasionally be seen in congenital hemolytic jaundice.

LIPOID GRANULOMATOSIS AND RETICULO-ENDOTHELIOSIS OF BONE

Numerous attempts in the past twenty years to classify the so-called xanthomatoses or lipoid granulomatous diseases which affect the skeleton and reticulo-endothelial system have led to much confusion and overelaboration of terminology The present discussion will follow the outline given below

Lipoid Granulomata	Nonlipoid granulomata	Reticulo-endotheliomata
Xanthomatosis with cholesterolemia (symptomatic and primary types)	Christian's disease	Reticulo-endothelioma, benign and malignant
Gaucher's disease	Eosinophilic granuloma	
Niemann Pick's disease	Boeck's sarcoid	

XANTHOMATOSIS WITH CHOLESTEROLEMIA

Patients with hypercholesterolemia may suffer from diabetes mellitus, obstructive jaundice, nephrosis or hypothyroidism. This form of *cholesterolemia is referred to* as symptomatic xanthomatosis. Patients with tuberous xanthomatosis of the skin also show a marked degree of hypercholesterolemia. This type of disease is often spoken of as *essential hypercholesterolemia* or primary xanthomatosis. In any of the foregoing conditions, lipoid granulomas composed of foam cells laden with cholesterol may be found. These may be deposited *in the tendon sheaths, joints, in the* bones, or in the viscera, such as the liver spleen and kidneys. Involvement of the bone is relatively rare in all of these conditions, but it does occur In the Chapter on *tumors of the tendon sheaths and joints,* a case is illustrated in a diabetic male, aged 44, who had a xanthomatous *deposit* in the lower end of the *humerus* (Fig 583) A case of essential hypercholesterolemia with bone involvement in a woman of 42 is illustrated below (Fig. 397) Both Rowland and Tannhauser believed that these xanthomatous deposits in bone are identical in nature with Hand-Schuller Christian's disease, but the modern tendency is to consider this disease as a granuloma, *not* necessarily associated with cholesterol disturbances.

GAUCHER'S SPLENOMEGALY

This is another form of xanthomatosis which is congenital in origin although its slow and insidious onset may delay clinical recognition for many years. The disease is accompanied by the storage of a lipoid kerasin, which is found in large phagocytes in the bone marrow spleen, liver lymph nodes, thymus, tonsils and other lymphoid tissues. The predominant features are splenomegaly rheumatic pains in the long bones, and pigmentation of the skin. In late cases the liver is also enlarged. The





Fig. 397 Roentgenograms and photomicrograph of multiple xanthomatosis in a woman aged 42.

disease is accompanied by anemia and leukopenia, and in severe cases, purpuric spots may appear in the skin. Females are affected more often than males and Pick



Fig. 398. (No. 49970) Roentgenograms of the femur in a girl aged 10 with typical Gaucher's splenomegaly. The patient was repeatedly treated between 1929 and 1933 for osteomyelitis before the discovery of the enlarged spleen. The roentgenogram depicts the characteristic flask like deformities of the femur with areas of bone resorption.

believes that the disease has a tendency to affect especially the Hebrew race.

Bone involvement is probably more frequent than is recorded. Of four patients with this malady recorded in the Mayo Clinic, bone changes were found in only one. In three cases recorded in the labora

tory characteristic changes in the long bones were found in two The long bones of the lower extremities and those of the pelvis are affected most frequently The femurs have a characteristic flared and rarefied appearance, usually compared to an Erlenmeyer flask (Fig 398) The affected cortex is narrow and wavy in outline, the cancellous structures are rarefied and pathologic fracture may occur (Fig 399) There is no periosteal reaction unless fracture takes place. Small areas of bone destruction in the medullary cavity may be mistaken for osteomyelitis.

The microscopic appearance of the lesions is characteristic. Large phagocytes varying from 20 to 100 microns in diameter with a vesicular nucleus and a finely granular or refractile cytoplasm are embedded in a stroma of reticulum cells and lymphocytes (Fig. 400) Phagocytosis of lipoids, chiefly cerebrosides (kerasin) forms the etiologic basis for the malady The disease rarely involves the soft parts and usually pursues a slow relatively benign course for twenty years or more.

Irradiation to the spleen and affected bones may be employed. Blood transfusions and other supportive therapy is of benefit. Splenectomy has been followed by symptomatic improvement in a few cases, but no definite cures have been effected.

NIEMANN PICK DISEASE

Niemann Pick disease is a rare form of lipoid disturbance appearing in infants. About 30 cases have been described in the literature. The disease is characterized by the storage of phospholipids in all the tissues, the lipoid laden foam cells giving to the affected regions a yellow color Enlargement of the liver and the spleen occurs in the first three months of life. The skin has a pale, yellow appearance and the superficial lymph nodes are enlarged. The blood cholesterol is elevated (in some instances as high as 650 milligrams per cent) Yellow deposits in the bone marrow have been described at autopsy but osseous changes are not a clinical feature of the disease, although patchy areas of osteoporosis are visible in the roentgenograms. Involvement of the lungs makes respiration difficult, changes in the nervous system lead to mental dullness and weakness. Death



Fig. 399 Roentgenogram showing pathologic fracture of the femur in a case of Gaucher's disease.

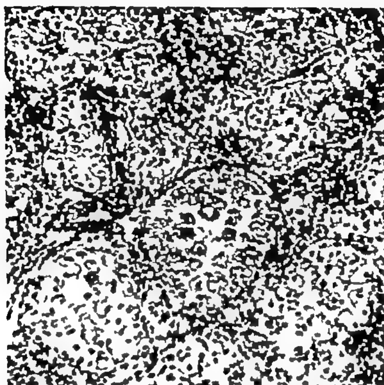
usually occurs in the second year of life. High caloric diet should be maintained, even if nasal feeding is necessary

CHRISTIAN-SCHÜLLER DISEASE

The clinical description of Christian's disease was formerly based upon the triad of symptoms including (1) defects in the membranous bones (2) exophthalmos, (3) diabetes insipidus. In the earlier reports emphasis was placed upon this triad and upon such findings as splenomegaly pigmentation of the skin, cholesteremia and

endocrine disturbances such as dystrophia adiposa genitalis and dwarfism. Racial and familial aspects of the disease were emphasized and it was thought that Hebrews were more susceptible than others.

The study of larger series of cases has shown that the osseous changes are among the most constant features in Christian's disease. Large defects in the membranous bones of the skull are usually manifest in the roentgenogram during the course of the disease (Fig. 401) In one case (Fig 402) which we have followed for a period of over nine years, the primary lesion was



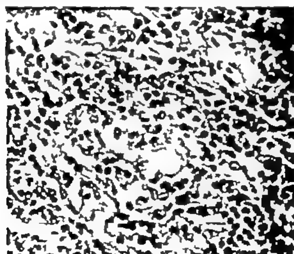


FIG. 400 (No. 49970) Low and high-power photomicrographs of the spleen in Gaucher's disease. The illustrations show large lipoid laden cells (Gaucher cells) embedded in a lymphoid stroma.

in the fibula. The first roentgenograms of the skull were interpreted as negative, although restudy of the films showed a slight osteoporosis. Nine years after the first roentgenogram was made (and without treatment during that interval) characteristic defects in the cranial bone appeared.

There are 17 cases of Christian's disease recorded in the laboratory All of them showed demarcated areas of bone destruction in one or more flat bones. In all but three the cranial bones were involved. The pelvic bones were affected in seven cases and in five instances the long bones showed similar rarefaction. In two cases the symptoms of onset were related to solitary lesions in the tibia or fibula.

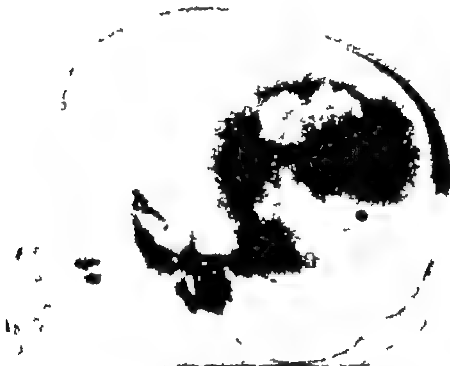


Fig 401. (No 46878) Roentgenogram of the skull showing characteristic defects in Christian's disease. Splenomegaly was a feature of this case.

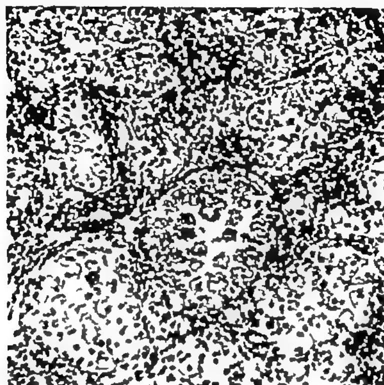
The rarefied areas in the roentgenogram have a characteristic appearance. The defects are usually large measuring several centimeters in their greatest diameter and clearly demarcated. In the membranous bones the lesions are confined to the diploe with thinning of the adjoining tables. In the other bones similar defects occur in the medullary cavity overlaid by narrowed cortex. Multiple foci of destruction are usually present. These may appear as separate defects or as confluent areas. There is no reaction in the neighboring periosteum.

The disease usually makes its appearance in the second year of life and is rarely seen after childhood. In our series the youngest patient was 2 years old and the eldest 14 One woman aged 42, with diabetes insipidus, showed multiple defects in the bones but was classed as symptomatic xanthoma The clinical manifestations in our cases (all of which showed bone involvement) were variable. Exophthalmos occurred twice, diabetes insipidus three times, pigmentation of the skin once, and splenomegaly was an outstanding feature in one case. In only one instance was the blood cholesterol elevated. In most of the reported cases the blood cholesterol is not elevated.

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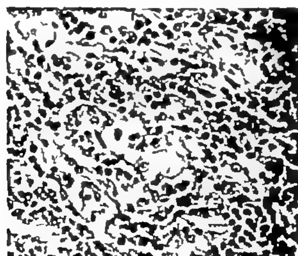


Fig. 400 (No. 49970) Low- and high-power photomicrographs of the spleen in Gaucher's disease. The illustrations show large lipoid-laden cells (Gaucher cells) embedded in a lymphoid stroma.

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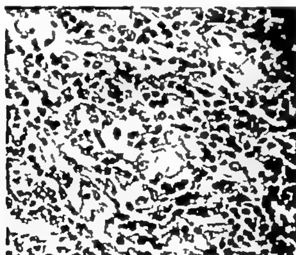


FIG. 400. (No 49970) Low- and high-power photomicrographs of the spleen in Gaucher's disease The illustrations show large lipoid-laden cells (Gaucher cells) embedded in a lymphoid stroma.

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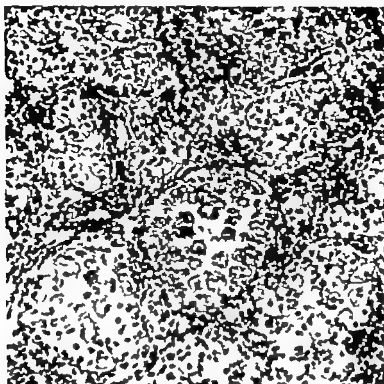
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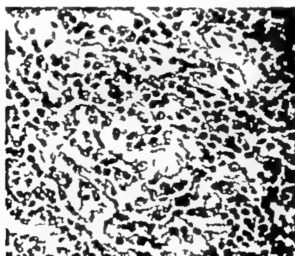


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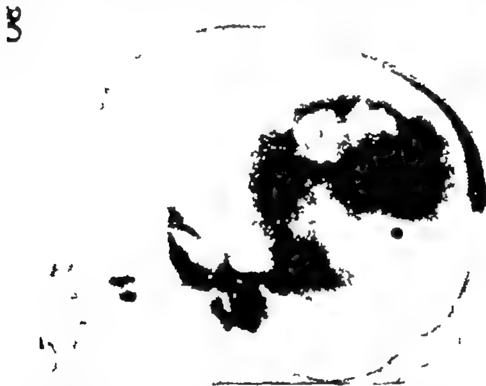


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volved and shortly thereafter severe diabetes insipidus developed and diffuse pulmonary infiltration. The lesions of the bone were irradiated and the diabetes insipidus controlled with intranasal applications of post pituitary powdered extract. The patient has been reasonably well during the past twelve years altho irradiation has been given for successive lesions in the mastoid, scapula and ribs.



FIG. 402. (No. 37070) Case of Christian's disease in a white male of four years Roentgenogram showing central defect of fibula before operation in September 1925 The tumor was primary in the fibula, which was resected for osteomyelitis in 1925 Small defects were present in the skull at that time. In 1934, nine years later the patient had multiple involvement of the skeleton.

The lesions are radiosensitive and the affected bones often re-ossify under such therapy Some of our cases proved rapidly fatal despite such treatment but in one case the disease progressed slowly over a period of ten years without therapy and the patient is still living.

The diseased tissue in the bone marrow is characterized by macrophages, eosinophils, plasma cells and lymphocytes. Mitotic figures are seen in the larger monocytes. The microscopic characteristics of so-called xanthoma—foreign-body giant cells, foam cells laden with lipoids, and blood pigment, occur but are more common in the spleen and lymph nodes than

in the bones, and are by no means constant. Histologically many large macrocytes, often binucleated and resembling Dorothy Reed cells, are the most important diagnostic feature. The appearance of foam



FIG. 403 A case of Christian's disease with multiple involvement of the bones of the extremities.

cells is not peculiar to this disease and they are often absent (Fig. 404)

EOSINOPHILIC GRANULOMA

Eosinophilic granuloma was first described by Fraser in 1935 who separated it as an entity from the group of so-called xanthomatoses, classified under the Hand Schuller-Christian disease. The lesion is usually solitary and affects a rib or flat bone, such as those of the pelvis or skull It occurs in childhood or young adults and is accompanied by low-grade fever and leucocytosis. The differential count may show from 5 to 10 per cent eosinophils. The affected bone is rarefied and its shell is expanded. The lesion is moderately tender and painful It is composed of granulomatous tissue in which eosinophils and macrophages predominate. Lymphocytes, foam cells and giant cells may also be present, along with *minute foci of necrosis.* The histiocytes phagocytize red blood cells and blood pigment. Lipoid phagocytosis is not a feature. *(Fig 405)*

The disease has an abrupt onset and the pain and swelling are soon accompanied by bone destruction, which reaches its maximum in a few weeks. Healing or cure following roentgen therapy or curettage is the rule.

Farber points out that eosinophilic granuloma occurring in children may contain undifferentiated eosinophils in their myelocytic form, and that the lesion may be confused with myeloma. In recent studies eosinophilic granuloma of the jaw has been associated with multiple defects in other bones.

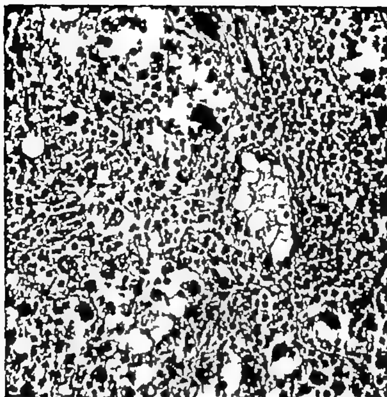


FIG. 404. (No. 49658) Typical Christian's disease in a child aged 2, showing large macrophages with foamy cytoplasm embedded in a stroma of eosinophils and lymphocytes. The picture simulates Hodgkin's disease or syphilis of bone.

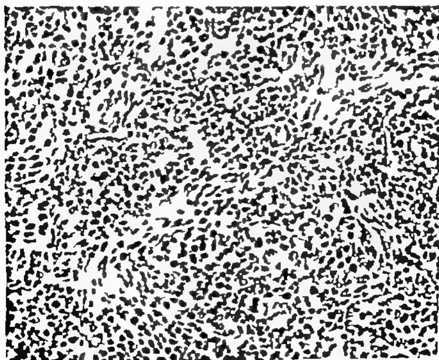


FIG. 405. Photomicrograph of typical eosinophilic granuloma.

SARCOIDOSIS (BOECK'S SARCOID)

Sarcoidosis is a disease of unknown etiology in which the clinical course and pathology suggest a chronic infectious etiology. Granulomatous, inflammatory changes resembling tubercles without caseation develop in the various organs of the reticulo-endothelial system and the skin. In some cases, the disease is widely disseminated and pursues a fatal course with involvement of the lungs, the nervous system, and, occasionally the heart. When the skin, lymph nodes or bone are primarily affected, the disease pursues a slow benign course, at times with spontaneous healing. There is no specific therapy.

Adults are usually affected. Several discrete nodules are present when the skin is involved. The cervical lymph nodes and those in the mediastinum are commonly affected. The osseous lesions produce foci of bone absorption, usually in the phalanges of the upper extremity. When the disease is systemic, enlargement of the lacrimal glands and the parotid may produce a Mikulicz's syndrome. Involutional changes in the lymphoid tissue, affected by sarcoidosis, results in the deposition of amyloid, and this disease is one of the causes of so-called primary amyloidosis. A significant number of patients have a falsely positive Wassermann reaction and an unexplained increase in the plasma globulins (3 to 6 Gm/100 cc.)

RETICULOSIS (LETTERER) RETICULO-ENDOTHELIOSIS (SIWE'S)

In this condition there is an extensive proliferation of the reticulum cells or histiocytes of the lymph nodes, spleen, bone marrow and liver. Other lymphoid organs, such as the thymus, the tonsils and the solitary follicles of the gastro-intestinal tract, may be affected. Involvement of the lungs and skin have been described. At first a group of regional lymph nodes enlarge, later the lymphadenopathy becomes generalized. Following this, hepatomegaly and



FIG. 408 Roentgenogram of eosinophilic granuloma of rib

splenomegaly may occur. Large histiocytes and macrophages tend to fill the sinusoids and to produce enlargement of the lymphoid germinal centers.

The age distribution is variable, ranging from infancy to senility. The sexes are affected equally. A preceding infection of the respiratory, gastro-intestinal or genito-urinary tract is recorded in many cases. Weakness, fever and hemorrhagic tendencies are usually present. The enlarged lymph nodes are discrete but not tender. Tumor masses develop in the bones and in the roentgenogram are destructive lesions (Fig. 408). Any of the bones may be affected. All cases have pursued a fatal course, varying from a few weeks to several years. At autopsy, the lymph nodes are discrete and grayish-pink or yellowish on sectioning. The enlarged liver or spleen on sectioning show grayish-yellow nodules of varying sizes. Microscopically, there is marked pleomorphism of the cellular elements. There are various types of macrophages and giant cells. The macrophages often have large, dense nuclei and appear malignant. There may be solid areas of reticulum-cell proliferation. The blood picture shows progressive anemia, monocytosis, and finally is characterized by a severe anemia and leukopenia of the aplastic type. The peculiarities of the disease are the involvement of the lymph nodes and the spleen by malignant reticulo-endothelial proliferation and the bone-destructive lesions. The monocy



FIG. 407 Boeck's sarcoid, involving the phalanges of both hands.



FIG. 408 Roentgenogram of malignant reticulo-endotheliosis involving the femur. This patient, a woman aged 52, had progressive bone involvement and died with generalized extension to the reticulo-endothelial system.

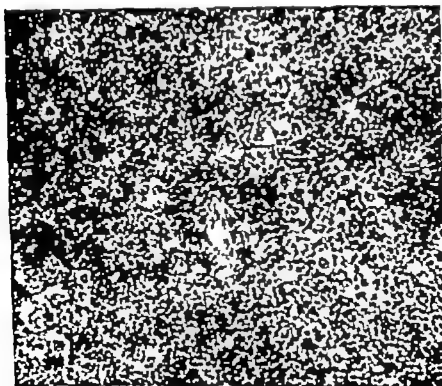


FIG. 409 Photomicrograph of reticulo-endotheliosis in a girl of 16 years. The lesion involved the cervical lymph nodes and the clavicle. The patient is alive 2 years after several courses of irradiation, but additional nodes have been involved.

tosis and increasingly severe anemia, and often the extreme ages of the patients affected (infants and individuals over the age of 75) are additional features. The condition resembles Hodgkin's disease but is distinguished from it by the presence of bone-destructive tumors and the marked pleomorphism of the histopathology

Foot and Olcott reported their case as nonlipoid histiocytosis. The largest cell contained phagocytized debris. No excess of lipoid could be detected in any of the involved tissue, nor did the abundant brown pigment of the lymph node give the reaction for iron.

Hertzog, in 1940 reported a case of reticulo-endothelial hyperplasia associated with increased storage of cholesterol. The patient was a 54-year old man whose clinical picture was that of splenomegaly with fatal aplastic anemia. At autopsy there was widespread storage of cholesterol, particularly in the lymph nodes and spleen The cholesterol content of the lymph nodes was 1 71 per cent and of the spleen 1.95 per cent. Normally the cholesterol content of the spleen is 62 per cent.

Microscopically fat droplets, stained with Sudan III and with nile blue sulfate, nearly obliterated the normal architecture of the lymph nodes and spleen and were present in the liver in increased amounts. The bone marrow was hypoplastic and contained a few clumps of large foam cells.

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21

Fibrosarcoma of Bone and Bone Involvement by Direct Extension of Sarcoma of the Neighboring Soft Parts

The osteogenic portions of the bone do not give rise to sarcoma of the true fibrospindle-cell type. The connective tissue tumors arising in this structure contain either fibroblasts of the fibro-osseous series with a tendency to bone formation (Fig 410) or precartilaginous connective tissue destined to form bone via cartilage (Fig 411) Fibrospindle-cell sarcoma arising in either the outer layers of the periosteum or in the adjacent soft parts may however invade the osseous substance and give rise to a tumor in which the predominant clinical manifestations are related to the bone Such bone involvement by extension from the soft parts is clinically very confusing, particularly when the bone changes are extensive. Even at operation or after pathologic examination of the tissue, it is often misinterpreted as a primarily osseous lesion

While from a pathologic standpoint this group of tumors usually has a structure indicating a connective tissue origin, the current conception that they are all products of the nonosteogenic layers of the periosteum, is erroneous. These tumors, on the contrary are far more variable in origin and may arise either from this investing portion of the periosteum or from fascia investing muscles, vessels or nerve trunks in the overlying soft parts. In fact, in the present series of 52 cases grouped clinically under fibrosarcoma of the bone, new growths with an origin in these various structures are all represented. The largest group of these neoplasms (31) show a histologic composition of fibroblasts, spindle cells, or small oat shaped cells, relating them to a single cycle of development in connective tissue, such as is found in the fibrous portions of the outer periosteum, the fascia or tendons. This group, which may be termed the fibrospindle-cell series, is a true pathologic entity and may be graded in its malignancy according to the degree of differentiation shown by the predominating cells.

A more varied and smaller group of these neoplasms must be differentiated from this larger fibrospindle-cell series. In this small group a careful analysis of the histologic structure shows the tumor to be arising from the nerve sheath (neurogenic sarcoma) or from the muscle (rhabdomyosarcoma) or from vessels (angioma) and hence the type of treatment and prog



Fig. 410 (No. 36784) *Fibroblastic tissue in bone laying down osteoid spicules in response to a low-grade infection* The fibroblasts are transforming into osteoblasts which are applied to the surface of bone newly formed from fibrous tissue

Fig 411 (No. 26392) Photomicrograph from an osteochondroma showing overlying strands of precartilaginous connective tissue *transforming* into cartilage *which is undergoing* calcification This precartilaginous connective tissue is the mother substance responsible for the resulting osteochondroma

nosis must be correspondingly different. This small and miscellaneous group of tumors, despite a varied source of origin, may secondarily invade bone because of proximity

The histologic composition in the new

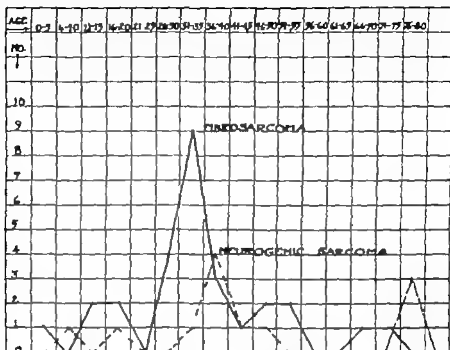


CHART 17 Chart showing the age incidence in 50 cases of so-called fibrosarcoma of the bone. The solid line indicates the tumors of the fibrospindle-cell series, the broken line tumors of the neurogenic series.

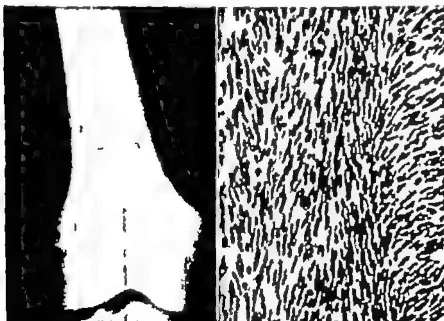


FIG. 412. Periosteal fibrosarcoma producing early bone erosion The roentgenogram shows a faint periosteal tumor and erosion of the cortical and cancellous bone beneath on the left. The photomicrograph shows the characteristic herringbone pattern of nuclei.

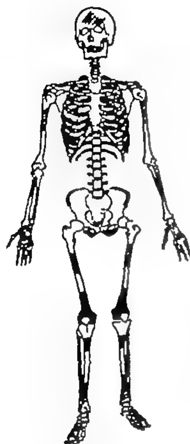


FIG. 413 Showing skeletal distribution in 50 cases of fibrosarcoma and neurogenic sarcoma of the bone The black areas indicate the most frequent sites, the checked areas, the common sites; and the diagonal lines the rare or occasional sites



FIG. 414. (No. 26884) Roentgenogram of a typical case of fibrosarcoma involving the shaft of the fibula. There is a large soft part shadow producing a faint periosteal reaction and splitting of the cortical layers of the bone. The patient was a white man, aged 29 giving a history of trauma, pain and tumor formation of 12 months' duration. Amputation was advised in this case The patient died of a tuberculous pneumonia 14 months after examination.

growth is a more reliable index to its clinical and pathologic behavior than is the anatomic location or apparent relationship to bone Assumptions regarding prognosis or treatment based upon proximity to bone disclosed by the roentgen rays or at exploration, or based upon the gross resemblance of the neoplasm to a fibroid substance are untrustworthy in this group of neoplasms. But conclusions can be drawn with a fair degree of accuracy after microscopic examinations which permit the lesion to be classified in either the fibrospindle-cell group, the neurogenic group or among tumors derived from other soft-part structures.

TUMORS OF THE FIBROSPINDLE CELL GROUP

Invasion of bone from without through direct extension by tumor usually indicates the presence of a sarcoma of the fibrospindle-cell group Such bone involvement is relatively infrequent and is recorded in only 1.5 per cent of the cases among approximately 2,000 neoplasms involving bone. The majority of the sarcomas in this group are not of a high degree of malignancy and the life of the patient can be safeguarded if

the proper diagnostic and therapeutic measures are carried out in time

CLINICAL FEATURES

Fibrospindle-cell sarcoma is a disease of adult life, occurring most frequently beginning with pain followed by the appearance of swelling and then by dysfunction of the limb In several instances a pathologic fracture occurred.

The swelling is smooth in contour and differs from the ordinary type of soft part



FIG 415 (No 23407) Anteroposterior and lateral views of a benign fibrous tumor involving the lower end of the femur in a white woman, aged 29 who gave a history of trauma, tumor and dysfunction of 10 months duration. The patient is alive 12 years following a primary amputation. Note the large soft-part shadow and the bone destruction resulting from invasion of the osseous substance from without. The microscopic structure of this tumor is shown in Figure 430

yond the age of 30 The age incidence is remarkable for a sarcomatous tumor and parallels more closely the distribution of carinomas among adults. The lower extremity is the site of predilection the region of the femur being most often involved. More rarely the upper extremity may be affected, and in exceptional instances the new growth may overlie the skull or ribs or be found within the pelvis (Figs. 413 and 414 Tables 81 and 82) The patients give a history of about one year's duration, be-

sarcoma in the depth of its location and in its firm attachment to the bone. Interference with function is also more rapid in the affected limb because of this proximity The tumor growth is fairly rapid and steadily progressive, producing a firm or rubbery mass. When the swelling is near the end of a bone, the growth may extend across the joint and involve a neighboring bone, a type of invasion which is exceedingly rare in truly osteogenic tumors. Although the regional lymph nodes may be enlarged,

Table 81 Differentiated Forms of Fibrospindle-Cell Sarcoma

Path. N	Race, Sex and Age	Location	Duration Mos.	Symptoms	Roentgenogram	Treatment	Microscopl	Result
28183	W F 46	Femur			Soft part shadow some bone destruction	Amputation July 14 1926	Spindle cell	Well 9 months
27113	W F 20	Femur up.		Pain, tumor		Excision, April 6, 1925 radium	Fibrospindle cell	Well over 2 yr
32?20	W M 43	Tibia, up.	17	Pain	Soft part shadow some secondary bone destruction	Curettement, Aug. 9, 1924; radium in wound	Fibrospindle cell	Dead 8 mos later
3?027	W F 30	Femur lw	3	Tumor	Slight bone involvement	Excisions, 1914 and 1919 amputation, 1919	Spindle cell	Dead 10 yr later
27?18	33	Femur	[illegible]	Pain, swelling 6 months	Secondary bone destruction	Exploration, Jan 23, 1919 roentgen rays, radium, March 12, 1919	Fibrosarcoma	Well 11 yr foll. exploration
32997	N F 53	Humerus, up.	36	Pain, trauma, tumor		Exploration, May 3, 1920	Fibrosarcoma	
31287	W F 34	Skull	2½	Slight pain, tumor	Secondary bone destruction	Exploration, Oct 14, 1929	Spindle cell	Dead 5 years later
27401	W F	Leg (knee)	36	Trauma, tumor	Large soft part shadow	Amputation, Nov 10, 1921; 2 excisions, roentgen ra and radium amputation	Fibrospindle cell	Well 8 yr
29249	M	Ankle reg.		Tumor	Soft part shadow secondary bone destruction	Exploration, April, 1917; radium, Oct. 1917 Coley toxins, amputation	Fibrospindle cell	Well 13 yr
29740	W M 40	Scapula		Tumor	Soft part shadow	Part. excision, April 1920; roentgen ra	Spindle cell	Disease progressing (11 yrs.)
29169	W F 23	Scapula	1	Tumor		Excision, Sept 1920 excision recurrence May 23, 1921; roentgen rays, radium	Fibrospindle cell	Well 3 yr following second operation
27534	W F 23	Ribs; 5th and 6th		Tumor		Excision, excision recurrence, November 1911; roentgen ra	Fibrospindle cell	Well nearly 10 yr following 2d operation
27753	W F 24	Femur, lw	24	Tumor pain and limp; one year		Exploration, February 1 1921 resection, February 4 1921	Fibrosarcoma	Dead 9 y following resection
27838	W M 49	Radius, lw	13	Tumor foll. sprain; 4 fracts.	Periosteal shadow with bone destruction	Amputation, Sept. 24, 1920	Fibrospindle cell	Well seven years
27347	W M	Femur lw	12	Tumor	Extensive bone destruction	Radium, Oct., 1920; curettement, amputation for recurrence Feb. 12, 1921	Spindle cell	Well over 9 y
20964	W M 29	Fibula, shaft	12	Trauma, pain, tumor	Soft part shadow some secondary bone destruction	Amputation advised	Fibrospindle cell	Dead 14 mos. foll. onset (Th. pneumonia)
20677	W M 30	Tibia, up.	48	Intermit. pain	Periosteal shadow some bone destruction	Exploration, Jan 1917; gold treat. Jan. 1919; exploration, Aug. 1920; amputation, November 22, 1920	Spindle cell	Well almost nine years following amputation
25483	[illegible] M 33	Femur lw	14	Pain, tumor	Periosteal tumor mass, small ant. bone destruction and formation	Amputation, February 14, 1920	Fibrospindle cell	Well 6 yr later
24536	W M [illegible]	Femur up.	17	Weakness	Soft part shadow bone destruction	Amputation, May 20, 1919	Spindle cell	Well over 8 yr
23407	W F 29	Femur lw	10	Trauma, tumor dysfunc. knee	Soft part shadow much bone destruction	Amputation, July 5, 1918	Fibrosarcoma	Well almost 12 y later
15723	W M 13	Tibia, up.	3	Pain, swelling, tenderness		Exploration, April 22, 1922; amputation, April 27 1922	Spindle cell	Lost
Surg. No. 9302 (9808)	W M 19	Femur lw	30	Trauma, joint effusion; 2d trauma; pain; swell.	Soft part shadow bone destruction	Exploration, Sept. 3, 1909; subsequent resection	Spindle cell	Dead, 11 y later

up.—upper
lw.—lower

TABLE 82.—UNDIFFERENTIATED FORMS OF FIBROSPINDLE-CELL SARCOMA

Path. No.	Race Sex and Age	Location	Duration in Mos	Symptoms	Roentgenogram	Treatment	Microscopic	Result
29872	W M 23	Lower femur		Pain, tumor	Osteoporosis, periosteal shadow	Explored, amputated, Dec., 1929	Oat-cell sarcoma	Living 3½ years
25908	W M 30	Tibia, upper	78	Trauma, pain, swelling latter 1 yr., 6 mo.	Soft part shadow considerable secondary bone destruction	Curettement, June, 1923; amputation, July 13, 1923	Oat-cell sarcoma	Dead 3 months following amputation
30748	W F 30	Upper femur		Pain, tumor	Soft part shadow bone destruction	Excision, June, 1932	Oat- and spindle-cell sarcoma	Dead of tumor
29691	W F 40	Tibia, left lower	96	Pain, tumor trauma	Soft part shadow slight secondary bone destruction	Exploration with cautery; amputation	Oat-cell sarcoma	Dead—lived 16 mos. following amputation
25276	W F ½	Humerus, lower	6	Tumor at birth	Large soft part shadow advanced secondary bone destruction	Excision, amputation, June 8, 1930	Oat-cell sarcoma	Well 9 yr. 11 mos., following amputation
38404	W M	Sacrum		Trauma, pain and tumor		Excision, radium	Oat-cell sarcoma	Dead 9 months following injury
34830	W M	Pelvis		Tumor		Resection of hip joint, May 10, 1919	Oat-cell sarcoma	Dead 2 years later
13850	W F 60	Humerus, lower	108	Fracture, subsequent swelling, pain, limitation of motion		Amputation, Oct. 22, 1912	Oat-cell sarcoma	Dead 2 years, one month, later
7563	W M 40	Femur lower	12	Trauma, pain, tumor		Amputation, Sept. 20, 1908	Oat-cell sarcoma	Dead 6 months later

metastases to the lymph glands have not been microscopically proved and probably do not occur. Metastases to the lungs are not uncommon.

ROENTGENOLOGIC FEATURES

Fibrosarcoma affecting bone resembles other forms of sarcoma of bone in its tendency to occur as a single lesion and to involve the regions of the lower femur and upper tibia. It differs from other malignant periosteal tumors in the size and character of its soft part shadow and in its tendency to destroy bone from without, inwardly. The one constant feature in the roentgenogram is this extra-osseous shadow which is more opaque than the cartilaginous masses seen in periosteal chondrosarcoma and less dense than the true bone formation seen in sclerosing osteogenic sarcoma.

The reaction of the underlying bone to the presence of the tumor is more variable. In the most easily recognized cases the bone is melted away from without, inwardly with little or no periosteal reaction (Figs. 414 and 415). In less typical cases strands of the periosteum which are split and raised may show varying degrees of ossification but these are never dense or conspicuous (Fig. 416). Calcification in the tumor substance is not the rule and is more typical of an aneurism, an old abscess of the soft parts, or of a rare chondroma associated with some bursa in the region of the joints. Occasionally however when the fibrous growth has become large and is not extremely rapid or after a course in deep roentgen therapy a slight degree of calcareous stippling will be observed.

The ratio of the soft part tumor to bone destruction is a helpful diagnostic point. Usually the extra-osseous shadow is large before much evidence of bone destruction is found. Occasionally however rarefaction and invasion of the marrow cavity are also pronounced so that there is a resemblance to metastatic carcinoma or osteolytic sarcoma of the osteogenic type (Figs. 417 and 418). In such instances,

however the size of the soft part shadow the disappearance of the cortex and the asymmetrical erosion of the marrow cavity give evidence that the bone is being destroyed from an external rather than an internal cause as in the truly central lesions. Benign giant-cell tumor and benign bone cyst should not be a source of confusion since these give evidence of their central origin by expanding a shell of cortical bone and rarely produce a soft-part tumor of any significant size The patient's age is also helpful



FIG. 416 (No. 25453) Anteroposterior and lateral views of a fibrospindle-cell sarcoma which is invading the bone The soft-part shadow has an unusual amount of calcified and osseous markings, most of which are due to the splitting and raising of the periosteum The patient was a white man, aged 53 who had suffered with pain and tumor in the lower end of the femur for 14 months. He has remained well over 6 years following amputation.

Gross Specimens

At *operation* the tumor is generally encapsulated, although occasionally it is found infiltrating muscle in the same manner in which it erodes and invades the bone. The tumor mass is firm and fibrous and often is arranged in whorls and strands which run in a number of divergent directions Occasionally the striation of the tumor is more regular (Figs. 419 and 420) and in the more rapidly growing neoplasms the mass may be fleshy or colored with hemorrhagic material (Fig. 421)

The kind and degree of bone involvement vary In some instances the tumor may be shelled away from the bone and the remaining osseous surface scraped clean with the knife. In other instances, the cortex has disappeared, the cancellous substance is invaded and broken and the central portion of the bone discolored by hemorrhage In rare instances, when the tumor is relatively benign and slow in growth, the entire cortex is melted away and the marrow cavity invaded, but the neoplastic tissue will be



Fig. 417 (No. 37088) A metastatic hypernephroma involving the shaft of the humerus. The area of bone destruction is central in origin and expands the cortex, which is undergoing destruction, symmetrically. There is little or no soft part shadow



Fig. 418. (No. 37614) An osteolytic sarcoma in the lower half of the femur producing a central area of bone destruction followed by pathologic fracture and escape of the tumor into the soft parts. The extent of the soft-part shadow is less than the area of bone destruction.

sharply demarcated from the firm reactive portions of the remaining bone

Dissection of the mass, particularly when the tumor is large does not often disclose its origin. In some instances it is clear that the relationship to bone is secondary the tumor shelling out easily and leaving a bare, denuded cortex with little or no evidence of erosion. In other cases the association with the bone is a more intimate one. The tumor may be definitely attached to the periosteum and may invade the cortex, gaining entrance to the marrow cavity On entering the marrow cavity it may penetrate up and down the long axis, splitting the bone and causing pathologic fracture In such cases, the only evidence against a primary osseous origin is the extent to which the soft parts are involved, the degree of extra-osseous involvement indicating that the tumor has had a beginning just without the bone.

In some of the tumors involvement of the joint cavity extension into adjoining bursae and into the neighboring muscles and involvement of the main nerve trunks or blood vessels suggest that the tumor is primarily of soft-part origin.

Microscopic Features

Since fibrous tissue derived from an earlier form of connective tissue is common to the stroma of nearly all organs, this type of fibrospindle-cell sarcoma invading bone does not differ histologically from similar



FIG 419 (No 38182) Gross specimen of a fibrosarcoma overlying and destroying the lower end of the femur in a white woman aged 46 which was successfully amputated. The cut surface of the specimen shows clearly the interlacing fibrous bundles, characteristic of this type of fibrospindle-cell sarcoma. The microscopic structure is shown in Figure 429



FIG. 420 (No 25453) Specimen from the amputated leg of the case of fibrosarcoma shown by roentgenogram in Figure 416. The cut surface of the tumor shows clearly the definite fibrous capsule and the relationship to the underlying bone The cortex is gradually being resorbed and the tumor has found its way into the marrow cavity Note the definite striations on the sectioned surface of the new growth, indicating a fibrous structure.

tumors in many other locations. Fibrospindle-cell sarcoma involving the joint capsule, tendons or ligaments, fibrous tumors arising from the outer vessel wall, and fibrosarcoma arising from the fascial planes in and about the muscles are a homogeneous group and differ in their fundamental pathology in no essential way from the new growths arising from the connective tissue framework of many of the internal organs.

It is possible therefore, to treat these sarcomas of the fibrospindle-cell group that secondarily involve the bone as a single pathologic entity regardless of the fact that their origin may vary

The microscopic structure of these neoplasms shows a definite cycle of histologic changes. The tumor springs from a small oat shaped mesenchymal cell which transforms into more elongated shape and thence into a prolonged fibroblast with an ever increasing amount of cytoplasm and intercellular material of the eosin-staining collagenous type In the more rapidly growing



FIG. 421 (No 24536) Gross specimen of a small spindle-cell tumor overlying the femur and invading the shaft of the bone in a white woman, aged 58 The patient has remained well over 8 years following an amputation. The fleshy tumor is shown adherent to the periosteum of the shaft of the femur



and malignant tumors, the microscopic picture is predominantly of the small, plump, spindle-cell type commonly known as the oat cell. The chief characteristic of this cell is the scantiness of its cytoplasm, the tightness with which it is packed, and the tendency for the nucleus to assume a rounded form and to undergo mitosis. Under the high power the cells (Figs. 425 426) resemble the primitive mesenchyme.

The oat cell is scarce among the less malignant tumors which are composed of spindle cells which become elongated into fibroblasts. When these spindle cells are tightly packed but fairly elongated and arranged in bundles or fasciculi, the type of

FIG. 422. (No 23407) Gross specimen of the fibrous tumor shown by roentgenogram in Figure 415. The fibroid tumor which is definitely encapsulated is shown invading the bone by pressure necrosis and is clearly demarcated from the neighboring osseous substance. The microscopic structure which resembled a benign fibroma is shown in Figure 430



FIG. 423 (No. 28276) A congenital oat-cell sarcoma in the lower end of the humerus in an infant 16 days old, who was treated by amputation following an exploratory excision The patient has remained well over 20 years. The roentgenogram shows the large soft part shadow and secondary erosion of the bone resulting in a pathologic fracture.



FIG. 424 (No. 28276) The amputated specimen indicating the cellular and hemorrhagic character of the tumor (See also Figure 425)



FIG. 421. (No 24336) Gross specimen of a small spindle-cell tumor overlying the femur and invading the shaft of the bone in a white woman, aged 58 The patient has remained well over 8 years following an amputation. The fleshy tumor is shown adherent to the periosteum of the shaft of the femur



FIG. 422. (No 23407) Gross specimen of the fibrous tumor shown by roentgenogram in Figure 415. The fibroid tumor which is definitely encapsulated is shown invading the bone by pressure necrosis and is clearly demarcated from the neighboring osseous substance. The microscopic structure which resembled a benign fibroma is shown in Figure 430

and malignant tumors, the microscopic picture is predominantly of the small, plump spindle-cell type commonly known as the oat cell. The chief characteristic of this cell is the scantiness of its cytoplasm, the tightness with which it is packed, and the tendency for the nucleus to assume a rounded form and to undergo mitosis. Under the high power the cells (Figs. 425, 426) resemble the primitive mesenchyme

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Fig 424 (No. 28276) The amputated specimen indicating the cellular and hemorrhagic character of the tumor (See also Figure 425)

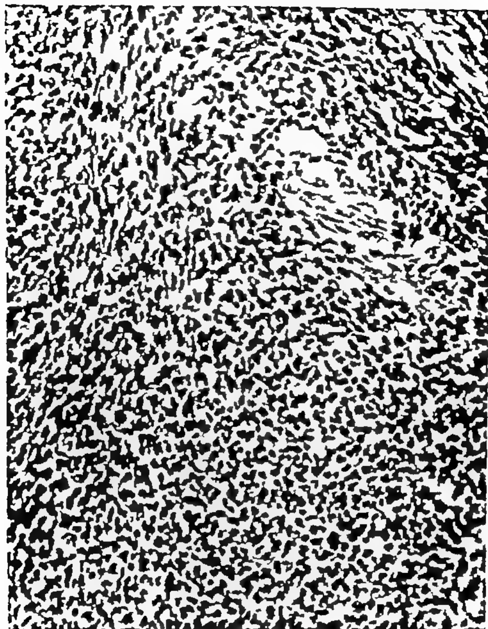


Fig 425 (No. 28276) Low-power photomicrograph indicating the tendency for the small oat cells to take on a more spindle shape and arrange themselves in definite bands or trabeculae

the tumor may be referred to as a spindle-cell sarcoma (Fig 427) When the spindle cell is largely replaced by fibroblasts and there is an increasing amount of intercellular substance the tumor may be called a fibrospindle-cell type (Fig. 428) When the fibroblast predominates and is scattered among a large amount of intercellular collagenous material, the tumor verges on a benign fibroma and is a low-grade fibrosarcoma (Fig 430) Scarcity or absence of tumor giant cells distinguishes these growths from sarcoma of the nerve sheath.

This gradual transition from oat cells to spindle cells to fibrospindle cells and to adult fibroblasts permits a definite grading upon which prognosis and treatment may be based. For this transition of cell forms represents the true histogenic cycle of the tumor This is indicated by embryologic studies of the primitive connective tissue surrounding the bone (Fig 431)

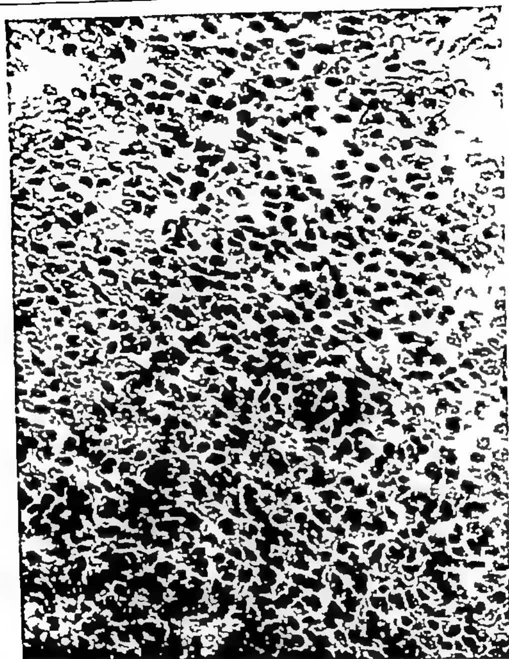


FIG 426 (No. 28276) High-power photomicrograph indicating the resemblance of the tumor to small, round-cell sarcoma under high power

In this primitive connective tissue or mesenchyme, the cellular elements are of the oat and spindle-cell types, with a scanty amount of intercellular substance resembling very markedly the less-differentiated oat and spindle-cell sarcomas.

When the tumors are of the oat-cell type with but scanty cytoplasm and with little or no intercellular substance, the neoplasm is always exceedingly malignant and therefore warrants the most radical treatment.

On the other hand, the more benign fibrospindle-cell and fibrosarcomas with fibroblasts and an abundant amount of intercellular substance are very slowly growing and metastasize late despite a tendency to recur locally They constitute another sub-group in which the grade of malignancy is definitely low

In between the oat-cell type and the

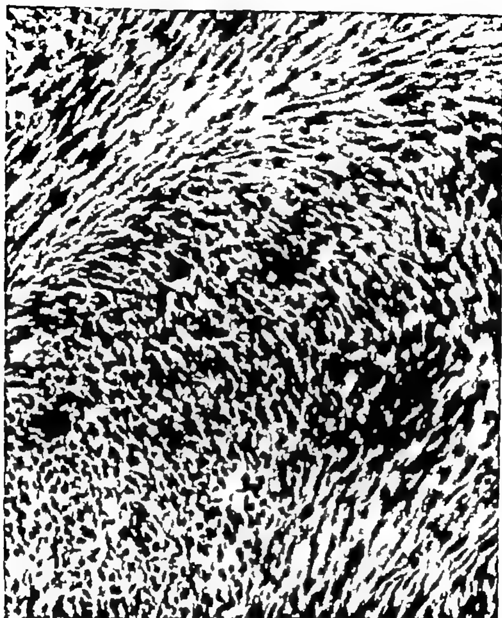


FIG. 427 (No. 31267) A spindle-cell sarcoma invading the skull of a white woman, aged 34, which resulted in death 5 years after an incomplete excision. The tumor is composed of characteristic fasciculi, and the predominant cells grade midway between the oat cell and fibroblasts, although both of these types are present.

more highly differentiated fibrosarcomas is the spindle-cell form which merges on the one hand with the oat cell type and on the other with the fibrosarcoma. If the cellularity in this type of tumor is marked and if there is any resemblance to the oat-cell type, it is best to be on the safe side and treat it radically

These various forms or grades of fibro-spindle cell sarcoma are distinguished from osteogenic sarcoma by the absence of cartilage or bone formation. Unlike the osteolytic variety of osteogenic sarcoma in which both cartilage and bone formation may be absent, the nuclei of these tumors show little or no tendency toward bizarre malignant forms and tumor giant cells are absent (Fig 432) The presence of small giant cells of the epulis type may occur but these are rare and are usually associated



FIG. 428. (No 27555) Low power photomicrograph of a fibrospindle-cell sarcoma, showing the tendency for the spindle cells to assume the characteristics of fibroblasts and lay down a definite amount of intercellular collagenous material. The prognosis of this grade of fibrospindle-cell sarcoma following a radical operation is extremely favorable. The tumor illustrated was from a radius of a white man, aged 49 who has remained well over 7 years following amputation

with the spicules of old bone undergoing necrosis.

These tumors of the fibrosarcoma group must also be distinguished microscopically from sarcoma of neurogenic origin which may secondarily invade the bone and which has quite distinct growth properties. The myxomatous substance, the elongated waving nucleus with the tendency to fibrillae formation and the enlarged tumor giant cell which are all typical of neurogenic sarcoma (Fig. 440) are not characteristic of these neoplasms.

PROGNOSIS AND TREATMENT

The prognosis and treatment of these tumors depend primarily upon an accurate microscopic analysis and secondarily upon the degree of bone invasion and upon the type of involvement of important vessels or nerves. From the microscopic standpoint it is essential to rule out the more malig

nant neurogenic and osteogenic sarcomas. This is not always an easy matter but a careful perusal of the photomicrographs included here together with the diagnostic

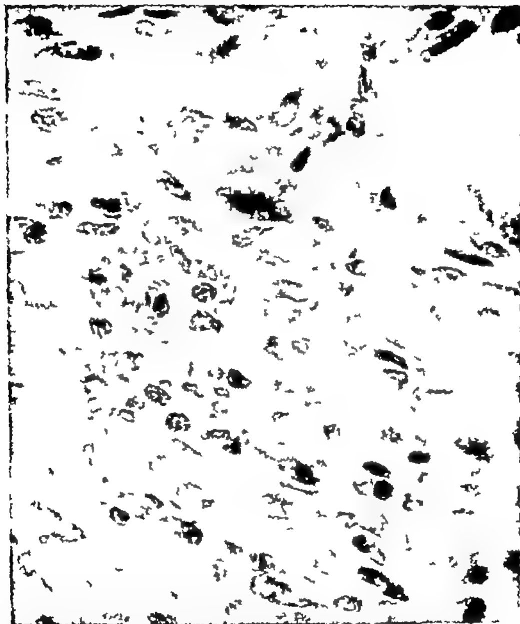


FIG 429 (No 38182) High-power photomicrograph of fibrospindle-cell sarcoma the gross specimen of which is shown in Figure 419 The illustrations show the variety of cells grading from oat cells to fibroblasts included in these types of tumors Note the tendency for the nuclei of the sarcomatous cells to assume a large vesicular form

points just mentioned will permit a fair degree of accuracy in this regard.

If the tumor is microscopically of the fibrospindle-cell series it is necessary to grade its degree of malignancy by determining whether it is of or closely related to the oat-cell type or whether it resembles or belongs to the more highly differentiated fibrosarcoma group In the present series of 31 cases, little difficulty was experienced in dividing these tumors into the undifferentiated and differentiated forms (Tables 81 and 82) This was done on a purely microscopic basis without knowledge or ref

erence to the clinical results. After this had been carried out, the clinical features and the results of treatment were tablulated for the two separate groups.

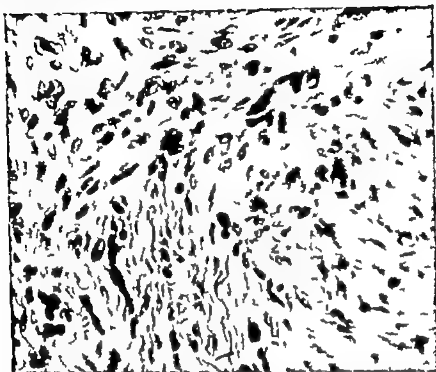


FIG. 430 (No 23407) Photomicrograph of the tumor shown in Figure 422. The tumor is composed predominantly of adult fibroblasts with a conspicuous amount of collagenous intercellular substance The nuclei are small and the tumor is essentially a rapidly growing fibroma.

Twenty two cases were placed in the differentiated fibrospindle-cell group The ages ranged from 12 to 58 years and the duration of the tumor from 1 to 48 months. None of these patients died within a period of 5 years after treatment, if we except one patient who succumbed to a tuberculous pneumonia and another on whom curettement followed by radium implantation was done. Even where no adequate treatment was given, as in case No. 31267 (Fig. 427) where the neoplasm invaded the skull, the duration of life reached five years. In all those cases treated by primary amputation in which adequate follow-ups are available, the patients were cured, and are living from 8 to 12 years after operation. Where local operation was done, the tumor invariably recurred, although in most instances life was prolonged beyond five years by an ultimate amputation or by further excision Repeated local operations, however have never proved sufficient to cure a case although a woman of 33 with a tumor in the region of the lower femur lived for 9 years before ultimately succumbing to lung metastases.

The value of deep roentgen and radium therapy is doubtful in these cases. The tumor is not radiosensitive, and after a local operation followed by roentgen or radium therapy the tumor has usually recurred. The outstanding conclusion that can be drawn is, that in face of marked bone involvement a local operation is insufficient in these tumors of the fibrospindle-cell group and even local operation plus roentgen and radium therapy is not sufficient to prevent a recurrence. The tumor however is slow to metastasize and

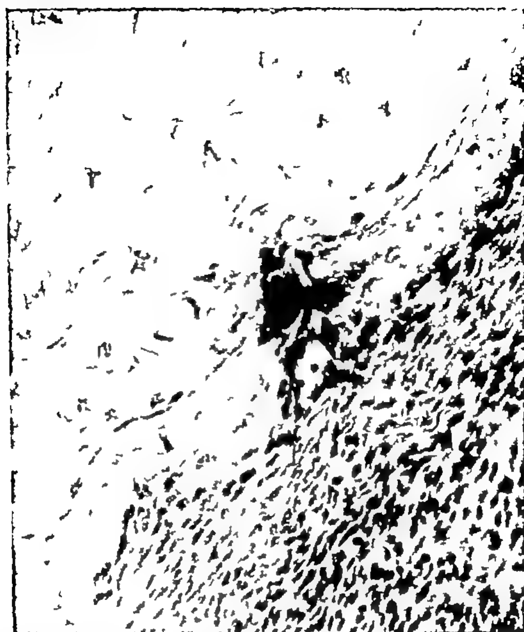


FIG. 431 (No 40934) Photomicrograph taken at the margin of a cross section of the humerus in a human embryo of 90 mm. The humerus is composed at this stage of calcified cartilage surrounded by a small rim of osteoid substance. Outside of this osteoid cuff is seen the primitive periosteum composed of oat and spindle cells or mesenchyme The photomicrograph supports the contention that the cycle of histogenesis in fibrosarcoma is from oat cell to fibrospindle cell to fibroblast

may be held in check from 5 to 10 years by repeated local operations with or without roentgen or radium therapy

Whether to combat the tumor by repeated treatment or insure its eradication by primary amputation depends upon its location, the degree of bone involvement and the age of the patient. In a vital location such as the skull repeated excision accompanied by roentgen or radium therapy is the only procedure possible. In the extremities if bone involvement is not marked and the cortex is still intact and if the important vessels and nerves are not included



FIG. 432. (No. 27852) High-power photomicrograph of an osteolytic variety of osteogenic sarcoma showing the bizarre nuclear forms characteristic of the very malignant tumor in contradistinction to the more benign fibrospindle-cell sarcoma.

in mass, local excision may be tried and an attempt made to save the limb in young adults. The microscopic pathology however must be checked at operation to rule out the oat-cell type and the mixed spindle and large-cell sarcoma of neurogenic origin If the local operation is done, it should be followed by deep roentgen therapy In our experience recurrence has invariably followed such procedure and it cannot be recommended as the treatment of choice When the tumor recurs, the limb should be promptly amputated.

When bone destruction is marked and important vessels and nerves are involved, the function of the limb cannot be saved and



FIG. 433 Roentgenogram of neurogenic sarcoma involving cancellous bone of the tibia in a man of 70 years.

the difficulty in eradicating the tumor with the consequent danger of recurrence justifies an amputation.

When the tumor is of the undifferentiated oat-cell type neither local excision nor roentgen therapy offers a permanent cure and if the location permits, a primary amputation should be done. These conclusions are supported by the data in Table 82. It will be seen that of the nine cases tabulated, only one (a tumor in the lower humerus present in an infant at birth) was permanently cured and in this instance a primary amputation was performed. These oat-cell tumors in infants, although microscopically identical with those in adults, are less malignant. In the case in which radium therapy was attempted it was of no avail and even primary amputation did not establish a cure in most instances.

NEUROGENIC TUMORS INVOLVING BONE

While the connective-tissue tumors of the fibrospindle-cell group that invade bone may arise at variable sites in fascia about such structures as bone and muscle, vessels, etc., it is possible that a group of tumors of quite different and more specific cellular composition may arise among these same structures overlying the bone and produce similar osseous involvement. Such tumors have a structure which identifies them with their tissue of origin. Among this group of tumors must be enumerated neurogenic sarcoma, angiomas, myosarcoma and lipomas and liposarcomas.

In the present series of cases there were fifteen tumors involving bone that could be related to the nerve sheath. These growths showed by wavy nuclei, wirelike fibrillae, myxomatous ground substance and tumor giant cells an origin from neural structures. They could also be related by microscopic appearance, clinical and pathologic behavior to a far larger group of subcutaneous and soft-part tumors of nerve sheath origin (*Geschickter**)

Clinically and in the roentgenogram these neurogenic tumors (Table 83) bear a close resemblance to the lesions of the fibrospindle-cell series just discussed. Pathologically also the similarity is marked. Like the fibrosarcomas, the neural tumors may have a marked fibrillar structure and show

* Geschickter C. F: Tumors of the peripheral nerves, Am. J Cancer 25 377 1935.

Table 83. Neurogenic Sarcoma Involving Bone

Path. No.	Race, Sex and Age	Location	Duration in Mos.	Symptoms	Roentgenogram	Treatment	Microscopic	Result
43743	W F [illegible]	Tibia, upper	19	Pain, swelling	Soft-part shadow roughening of bone	Roentgen therapy, complete excision, Dec 1930	Neurogenic	
43483	W M 23	Tibia, upper	73	Pain, swelling	Soft-part shadow large area bone destruction	Amputation, Aug 1930	Neurogenic	
38722	W M 73	Fibula, upper	54	Pain, tumor		Curettement, Dec., 1926; radium; P O x-ray	Neurogenic	Dead 1 year
34504	W F [illegible]	Fibula	13	Pain along distribution of nerve; swelling	Soft-part tumor bone erosion	Refused treatment		
36721	W M 78	Femur, lower		Pain, tumor		Amputation, Jan 29, 1923	Neurogenic	Dead 7 months later
33249	W F 16	Tibia, upper			Soft-part shadow secondary bone destruction	Amputation, Oct. 21 1924; pre-op. roentgen rays, Feb. 23, 1924	Neurogenic	Well 3 years and seven months
34675	W M 44	Ischium and groin	3	Pain, swelling	Bone erosion	Radiation (radium); excision, May 1921	Neurogenic	Dead 11 months later
33028	W M 46	Femur, lower	4	Pain, pathologic fracture	Soft-part shadow extensive bone destruction	Exploration, Sept. 11 1923; roentgen rays, amputation, September 24, 1923	Neurogenic	Dead 14 months later
30486	W M	[illegible], skull	1	Pain, swelling	Bone destruction; skull	Exploration, Dec. 12, 1921; radium, January 1922	Neurogenic	Dead 2 years later; metastases, extension of tumor through dura to brain, skull and vertebra involved with tumor
26593	W M	Femur, lower	10		Soft-part shadow advanced secondary bone destruction		Neurogenic	Dead
26178	W M 32	Femur, lower				Resection, May 20, 1920; bone graft	Neurogenic	Dead 7½ months later
2[illegible]99	W M 27	Femur, lower	3	Tumor, pain, pulsation	Soft-part shadow secondary	Irradiation, March, 1920	Neurogenic	Dead 3 months later
17671	W F 65	Radius, upper	6	Pain, tumor	Soft-part shadow secondary destruction of upper radius	Amputation, June 12 1916	Neurogenic	Dead 6 months following operation

P. O.—Post-operative
Pre-op.—Pre-operative



FIG. 434 (No. 30855) A case of neurogenic sarcoma arising in the soft parts of the buttocks of a white boy aged 7 and invading bone. (A) shows the original tumor which was removed by excision (B) the gross specimen after removal. Note the lobulated character of the growth and its gelatinous mucoid appearance (C) shows the metastasis to the frontal bone which invaded the dura and penetrated into the brain substance. The vertebrae were also involved by metastases. The patient died 2 years after the initial operation despite radium treatments.

under the microscope many spindle cells (Fig 440) As in these fibrous growths which show a continual gradation from the benign fibroma to the most malignant spindle-cell forms, there is also a gradual transition among the neural tumors from the benign neurinomas to the most malig forms of neurogenic sarcoma.

Unfortunately for the treatment o *forms of sarcoma most frequently loca* in the extremities, the pathologic distin between tumors of the fibrospindl series and tumors of the neurogenic s is not easily made. The histological g tions from the more benign fibrom the more malignant fibrospindle and cell sarcomas in contrast to the grada between the more benign neurinomas the more malignant neurogenic sarc further complicate the problem. As a r much confusion has arisen

In those neurogenic tumors which in bone the more malignant and cellular f predominate and in no instance of series was there difficulty in disting ing these sarcomas from the benign rinomas. This cellular structure is in k ing with the invasive character of growth which has forced its way into osseous substance. While thus easily tinguished from the benign neurino careful microscopic study was nece to differentiate these growths from f spindle-cell sarcoma. However that microscopic distinction was success made is borne out by the clinical feat and results of treatment. The clinical low-ups show that once neurogenic sarc has invaded bone the chances for cur matter how radical the mode of treatm are practically nil.

CLINICAL FEATURES

While the most important points of tinction are not clinical or roentgenol but relate to the pathology and to the sponse of the neurogenic tumors to tr ment, these neoplasms nevertheless pre certain clinical peculiarities. The age the patient is usually well over 30 (f 32 to 75) and the duration of clin symptoms averages over one year In c one case of neurogenic sarcoma inv ing bone in this series was a child affect



Fig. 435 (No 33028) Roentgenogram of neurogenic sarcoma occurring in a white man, aged 26 who died 14 months after amputation. Lateral view shows the soft part tumor invading the popliteal space. Opposite this point the entire osseous substance of the femur had been destroyed and a pathologic fracture has occurred



Fig 436 (No 26593) Roentgenogram showing a neurogenic sarcoma which is invading the femur from without There is a soft part shadow just above the lateral femoral condyle and opposite this point the cortical and cancellous bone is being destroyed The patient died with pulmonary metastases, two years after amputation For microscopic structure see Figure 440



Fig. 437 Roentgenogram of neurogenic sarcoma proliferating along the interosseous membrane and involving the fibula and tibia.

This was in a white boy of 7 who had a tumor in the soft parts of the buttocks (Fig 434) and in this instance, the osseous involvement differed from the other cases in that the skull and the vertebrae were affected by metastases.

The bone involvement as shown in the roentgenogram (Figs. 435 436, 437) is more pronounced in neurogenic sarcoma than in fibrospindle cell sarcoma. Pathologic fracture may occur (Fig. 435) and the lesion may resemble metastatic carcinoma or osteolytic sarcoma of central origin. In other respects the roentgenograms bear a remarkable resemblance to those seen in fibrosarcoma. The striking changes in the length and structure of the bone which may be brought about by the benign types of Von Recklinghausen's neurofibromatosis are not included in this group.

Symptoms referable to nerve involvement such as tingling or pain along the distribution of the nerve trunk were not marked in this group and once the tumor developed to an appreciable size the disturbances referable to the bone dominated the clinical picture.

Pathology

These neurogenic tumors are less firm and more fleshy than fibrospindle-cell sarcoma. They have either a soft and beefy red appearance or are composed of a gray translucent jellylike myxomatous substance. The fleshy tumor besides finding its way into the bone is locally disseminated along the neighboring nerve trunk and this structure shows a decided tendency to be diffusely involved by multiple discrete or lobulated tumors of this character (Fig 435 *B*) When the marrow cavity of the bone is invaded, the white translucent areas of tumor infiltration are accompanied by regions in which hemorrhagic and honeycombed cavities are opened up in cancellous bone (Fig. 439) The periosteum is raised by the tumor growth, and the joint cavity in the vicinity may be involved (Fig 438) a complication rare in osteogenic sarcoma but occurring in fibrosarcoma affecting bones. Peers* has reported a case arising in the medullary cavity of the ulna.

Under the microscope strands of tightly packed elongated spindle cells are very common and give these tumors a super

* Peers, J H.: Primary intramedullary neurogenic sarcoma of the ulna, Am. J Path. 10: 811 1934.

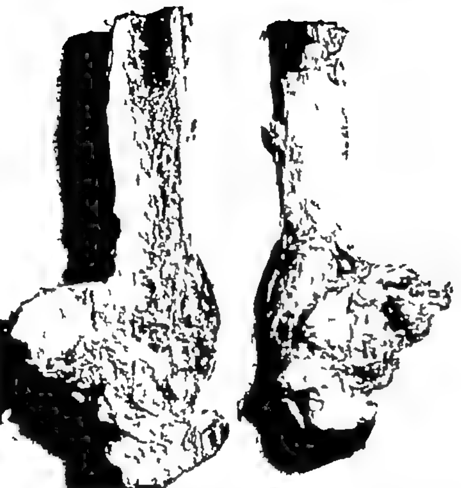


Fig. 438. (No. 43482) Gross specimen of the case shown in Figure 444. The specimen includes the tumor mass in the knee joint which is shown attached to and invading the lower end of the femur The original tumor arose opposite the head of the tibia (for microscopic structure see Fig. 444)

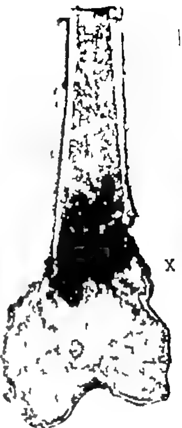


Fig. 439 (No. 26593) Gross speci men of the case shown in Figure 436 The tumor has gained entrance into the marrow cavity through the eroded cor tex at the site marked \ A portion of the tumor infiltrating toward the epiphysis is of a white myxomatous charac ter while, above hemorrhagic spaces have been opened up in cancellous bone.

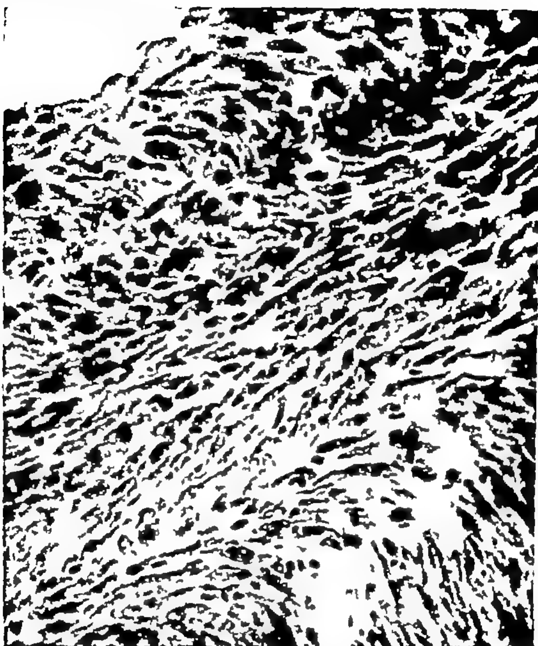


FIG. 440 (No 26393) Photomicrograph of a section taken from a specimen shown in Figure 439 This neurogenic tumor although having a superficial resemblance to fibrosarcoma, shows myxomatous areas (lower right hand corner) a tendency for the cells to line up in rows and tumor giant cells.

ficial resemblance to the fibrospindle cell sarcoma (Fig. 441) There is, however a faintly staining myxomatous substance that is present in fairly conspicuous areas interspersed among the spindle-cell bundles. Within these myxomatous areas are found degenerating cells with small nuclei and a faintly staining rounded cytoplasm (Fig 443) or small glia like elements. The elongated spindle cells also present definite peculiarities. The nuclei are generally longer and more deeply staining than those found in fibrospindle-cell sarcoma and are rippled or waved (Fig 441) The appearance of large tumor giant cells in the section and the tendency for the cells to line up in parallel rows are important diagnostic points the one indicating a high degree of

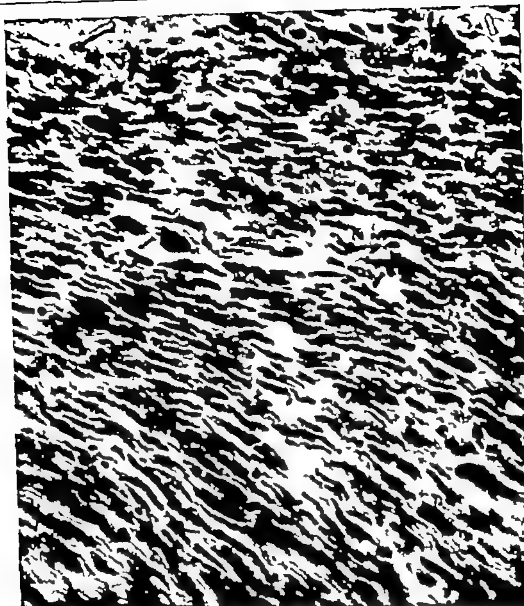


FIG. 441 (No. 26593) Photomicrograph of another section from the specimen shown in Figure 439 In this area, in addition to the tumor giant cells, the nuclei have a wavy or rippled appearance, characteristic of neurogenic sarcoma. There are definite formation of fibrillae and a very scanty amount of intercellullar substance Again the cells are lining up in definite rows.

malignancy and the other recalling the growth characteristics of regenerating neurilemma sheath (Figs. 444 and 445)

Like fibrospindle-cell sarcoma these neurogenic tumors may be microscopically graded. Frequent myxomatous areas about which clumps of elongated nuclei in cells of the neurilemma type are found in a palisade arrangement are more typical of a benign neurinoma and are prominent in the neurosarcomas with a slower rate of growth. So are the so-called reticular areas in which cells with small nuclei are loosely scattered. As the tumor takes on a high degree of malignancy large pleomorphic nuclei are seen scattered through the tissue and the spindle-shaped cells become more tightly packed. In the highly malignant cases tightly packed spindle cells with sharply pointed nuclei crowd out the myx



Fig. 442. (No. 36721) Photomicrograph showing myxomatous areas of a neurogenic sarcoma. The patient was a white man, aged 75. The tumor occupied the popliteal space. It invaded the muscles and fascia, destroyed the femoral shaft, involved the external condyle and was beginning to invade the upper end of the tibia. The cavities in the bone were filled with a gray translucent material, typical of neurogenic sarcoma. The patient died seven months after amputation.

omatous areas and the tumor giant cells take on a bizarre appearance.

Prognosis and Treatment

The prognosis in neurogenic sarcoma even after a primary amputation is not good. These neoplasms arising from the deep lying nerves, and invading bone recur promptly after local operation and are not radiosensitive. Once osseous invasion has taken place a primary amputation following biopsy is the treatment of choice. There is only one cure extending over five years in this series and this was in a young individual with a tumor invading the upper tibia who was treated by amputation following a preoperative course of deep roentgen therapy. Microscopically also this

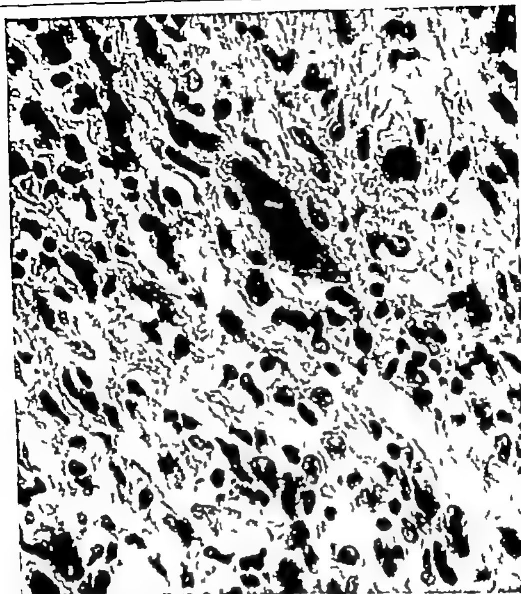


FIG. 443 (No 36721) A fibrous area in a malignant nerve-sheath tumor In addition to the cells resembling fibroblasts, tumor giant cells are present. A tendency to form fibrillae and areas of reticulation (typical of neurogenic sarcoma) is seen.

tumor was an exception, being largely neurinomatous (Fig 445) The other eight cases which were satisfactorily traced, all died within two years of date of treatment, despite the fact that amputation or radical resection was done in six instances. Irradiation with x rays or radium was used in three of these fatal cases. Where local operation was performed the tumor recurred promptly and in one instance (Fig 449) where operation was not performed because of suspected pulmonary involvement by tumor metastases, death followed within two months, although the patient had symptoms referable to the bone for only five months previous to examination

While the present series is too small to permit conclusions in regard to therapy the results observed are in accord with a larger series of cases of neurogenic sarcoma, which occurred in the soft parts without osseous involvement. From these combined studies it can be said that the cellular forms of neurogenic sarcoma are rarely

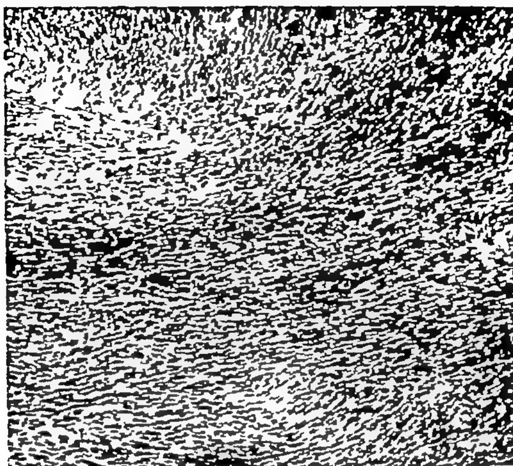


FIG. 444. (No. 43482) Photomicrograph of a cellular neurogenic sarcoma. The photograph shows the presence of myxomatous areas, the alignment of the cells in definite rows and the large anaplastic nuclei, typical of neurogenic sarcoma.

cured, either by extensive local operation or by irradiation with deep roentgen rays or radium. The best results are achieved by early primary amputation and even with this radical form of treatment, permanent cures are not numerous.

This gloomy outlook in neurogenic sarcoma involving bone is in marked contrast to the results obtained in the fibrosarcoma group described in the first part of this chapter. In this less malignant group it will be recalled, cures extending beyond five years were the rule, even after late amputation following recurrence. The contrast in the results between these two otherwise similar groups of tumors emphasizes the importance of distinguishing between them. Heretofore all of these neoplasms invading bone from without by direct extension have either been loosely classed as parosteal fibrosarcoma or confused with primary sarcoma of bone. In fact, most of the cases reported here were originally diagnosed from the clinical and pathologic standpoint as primary sarcoma of the bone. It is important to bear in mind that these tumors of nonosseous origin that invade bone by direct extension have a variable pathology. When in the fibrosarcoma group and not of the oat-cell type, the outlook for five-year survival with proper treatment is exceedingly favorable if not certain (86 per cent of the cases are living over five years). When the neoplasm is of the neurogenic sarcoma type and involves bone, the outlook is practically hopeless if the lesion is of a very cellular type, and even if the structure of the tumor is largely

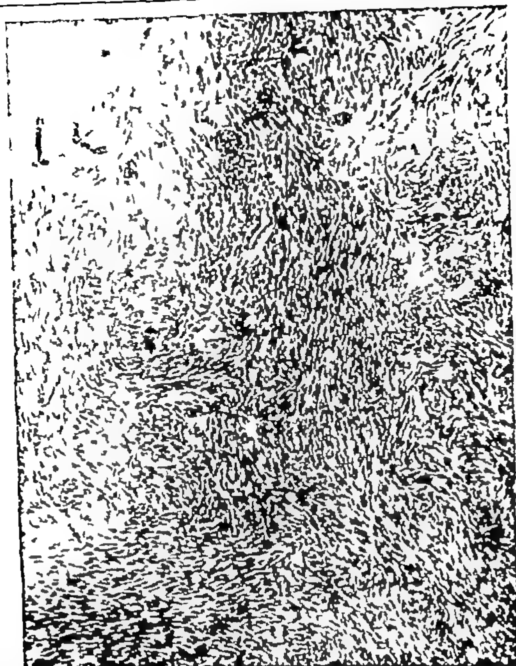


FIG. 445 (No 35248) Transitions in neurogenic sarcoma from the more benign neurinomatous type of malignancy to the most malignant forms. The early malignant change in the neurinoma is shown. Myxomatous tissue predominates and the nuclei have a palisade arrangement.

neurinomatous, radical amputation is indicated. In both of these groups of tumors just mentioned, the prognosis and indication for treatment differ from primary sarcoma of bone where the outlook for a cure is usually better than in tumors of the malignant neurogenic group but worse than in neoplasms of the fibrosarcoma group.

OSSEOUS INVASION BY MISCELLANEOUS TUMORS OF CONNECTIVE-TISSUE ORIGIN

In addition to the fibrosarcomas and neurogenic sarcomas producing skeletal involvement there may be in rare instances a similar clinical picture caused by some un

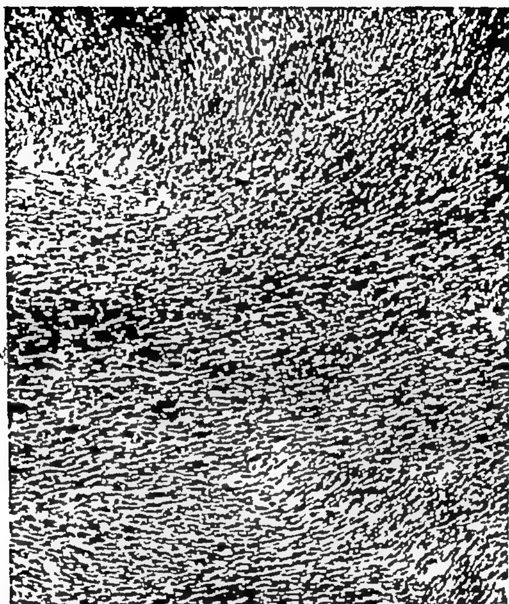


Fig. 446 (No. 43482) Photomicrograph of a more malignant neurogenic sarcoma showing crowding of the nuclei, anaplastic, large nuclear forms, and scarcity of intercellular substance

usual form of tumor of the connective tissue series.

In a review of 2,000 neoplasms involving bone, in which all cases with adequate data had been definitely classified, there were found eighteen cases which could not be classed as either primary bone tumors or metastatic to the skeleton from other organs. These were neither of the fibrosarcoma nor neurogenic group The majority were angiomatous, one myosarcoma and the remainder lipoma or liposarcoma. These rare neoplasms involving bone are briefly reviewed here.

Angioma of the Bone

From the literature, particularly of the nineteenth century it would appear that tumors of the hemangioendothelial or hemangioma group are fairly common but these older reports have in a large measure been discredited since they included many cases, either of carcinomatous metastases to bone,



FIG. 447 (No. 28593) Very malignant neurogenic sarcoma showing a microscopic picture predominated by crowded, elongated nuclei and tumor giant cells.

vascular forms of osteogenic sarcoma or neoplasms now recognized as Ewing's sarcoma or multiple myeloma. The verified cases of hemangioma appearing in the literature have been collected by Bucy and Capp and by Geschickter and Maseritz in 1938.

Twelve benign hemangiomas of bone (Figs. 449 through 454) were available for study. These growths are most frequent in young adults but children may be affected. In the long bones multilocular areas of destruction expand the shell of bone in one direction to paperlike thinness, but usually do not extend deeply into the medullary or cancellous spaces. The shaft is usually involved. In the skull and spine the rarefaction produced often has a honeycombed appearance and delicate, radiating spicules of new bone may be formed. In the long bones, the cases in our series presented characteristic features. One of these was of the cavernous type, occurring in a male aged 25 in the upper right humerus, with

Bucy, Paul C., and Capp, Charles S. Primary hemangioma of bone. Am. J. Roent. & Rad. Therap. 23: 1, 1930.



FIG. 448 (No. 25888) A neurogenic sarcoma invading bone and producing pulmonary metastases. Symptoms referable to the involved femur were present only five months, when the roentgenogram of the chest showed evidence of metastases. The patient died two months after the date of taking the films.

FIG. 449 (No 25892) A primary cavernous hemangioma of the upper end of the humerus, occurring in a white man, aged 25 following four years after trauma. The patient is living twelve years after a curettage and has full function of the arm (case of Dr James Hitzrot) The roentgenogram illustrates the characteristic soap-bubble effect produced in the periosteal and cortical zones. There is no destruction in the marrow cavity



Fig. 450 (No 25892) Photomicrograph showing an area with dilated blood spaces lined by endothelium about which connective-tissue elements are proliferating (See also Figure 449.) This is the typical structure of a cavernous hemangioma, more common in the subcutaneous tissues.



Fig. 451 (No. 38052) A case of primary capillary hemangioma in the lower end of the ulna occurring in a white youth, aged 20 following eight months after trauma. The patient is living five years after a resection The roentgenogram shows the characteristic soap-bubbles.





Fig 448. (No. 25888) A neurogenic sarcoma invading bone and producing pulmonary metastases. Symptoms referable to the involved femur were present only five months, when the roentgenogram of the chest showed evidence of metastases. The patient died two months after the date of taking the films.

Fig. 449 (No. 25892) A primary cavernous hemangioma of the upper end of the humerus, occurring in a white man, aged 25, following four years after trauma. The patient is living twelve years after a curettage and has full function of the arm (case of Dr James Hitzrot) The roentgenogram illustrates the characteristic soap-bubble effect produced in the periosteal and cortical zones. There is no destruction in the marrow cavity





FIG. 450 (No 25892) Photomicrograph showing an area with dilated blood spaces *lined by endothelium*, about which connective-tissue elements are proliferating. (See also Figure 449.) This is the typical structure of a cavernous hemangioma, more common in the subcutaneous tissues.



FIG. 451 (No. 38952) A case of primary capillary hemangioma in the lower end of the ulna occurring in a white youth, aged 20 following eight months after trauma. The patient is living five years after a resection. The roentgenogram shows the characteristic soap-bubbles.



Fig. 452. Roentgenogram of a capillary hemangioma of the humerus made before treatment in 1933 The patient was a girl, aged 8



Fig. 453 Roentgenogram of lesion shown in Figure 452. This film was made in 1937 after two curettings, irradiation and the insertion of a bone graft There had been two pathologic fractures.

pain of two years duration following a trauma four years previously The roentgenogram showed a peculiar soap bubble effect extending into the periosteal zone and producing only slight bone erosion. At operation a thin bone shell was found and the tumor beneath had the appearance of an altered blood clot. The section showed a loose connective tissue stroma with dilated blood sinuses lined by endothelium and numerous peculiar connective-tissue cells suggestive of sarcoma (see illustrations) This case was reported in the Annals of Surgery April 1917 by Dr James M Hitzrot of New York, who appended a bibliography on Vascular Tumors reported in the older literature. Although only a curettage was done in January 1916, the patient (who is a surgeon) was reported as leading an active life with full use of the arm in 1928.

An angioma of the capillary type (Fig 451) occurred in the lower ulna in a white male aged 20, following an injury to the right wrist eight months previously This case is recorded as No 849 in the Bone Registry of the American College of Surgeons. The tumor grew rapidly and was of soft consistency The neoplasm had the same loose soap bubble effect in the roentgenogram. The lesion was resected in Sep-

Hitzrot, J M. Haemangioma cavernosum of bone, Ann. Surg 45 477 1917

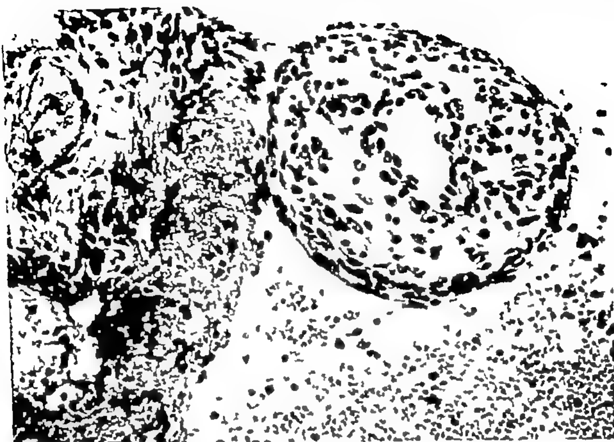


Fig. 454. Photomicrograph of the lesion shown in Figures 452 and 453

tember 1926, and in the gross was composed of numerous irregular hemorrhagic cavities embedded in a white fibrous substance The sections showed a mass of dilated capillaries lined by endothelium and surrounded by young connective tissue cells embedded in adult fibrous tissue. The patient was last reported well in September 1931, five years after operation

Four more cases of angioma of the long bones are included, three of the capillary type affecting the humerus and one of the femur The tumor involving the femur occurred in a girl of 17 who had complained of rheumatic pains in this region for more than a year In the roentgenogram (Fig 460 and 461) there was an asymmetrical cystic tumor with a thin shell of bone typical of angioma. The lesion healed under deep roentgenotherapy and the patient has remained well for a period of 10 years. No biopsy was obtained. Three additional hemangiomas occurred in children (two in the upper humerus and one in the radius) and resembled multilocular bone cysts. Five angiomas affected the skull and two the vertebrae. Angiomas of the skull are usually primary in the meninges and invade the bone by direct extension They may be primary in the scalp In the spine more than one vertebrae may be affected. In both skull and vertebrae the tumor may be accompanied by neurologic symptoms. In one of our cases the tumor invaded the fourth, fifth and sixth cervical vertebrae and compressed the spinal cord. The patient had attacks of coma and epilepsy and the symptoms were attributed to hysteria when the patient was first examined.

Pathology Angioma of bone often shows a partly cystic tumor with hemorrhagic contents beneath a thin shell of cortical bone. Current jelly" material may fill the entire portion of the medullary cavity occupied by the new growth. Microscopically capillary cavernous or angioblastic

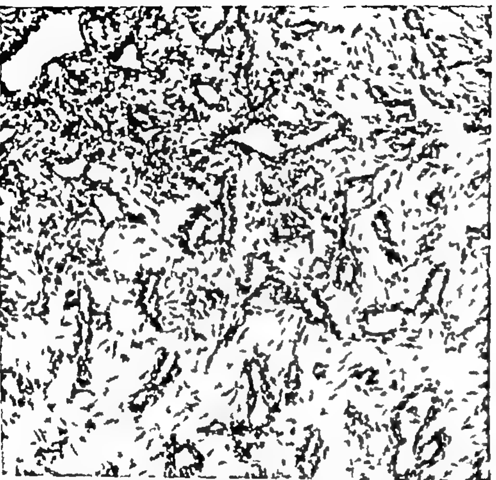


Fig. 455 (No 38952) Photomicrograph showing an area of dilated capillaries, lined by endothelium and surrounded by a loose connective tissue stroma. The tumor occurred in the lower ulna and was cured by resection



Fig 456 (No. 15221) A case of primary capillary hemangioma in the lower end of the humerus, occurring in a Negro aged 52, following three years after trauma. The patient was discharged well after a local excision performed in 1911 and has not been traced since.



Fig. 457 Angioma of the os calcis.



Fig. 458. Angiosarcoma of the fifth metacarpal bone



Fig. 459 Photomicrograph of angiosarcoma shown in Figure 458.



FIG. 460 (No 45686) Angioma of the bone occurring in the femur of a girl aged 17 The roentgenogram emphasizes the characteristic subcortical location of the tumor and the thin expanded shell of cortical bone This lesion was successfully treated by roentgenotherapy

features may predominate. The cellular angioblastic tumors are rare Angiosarcomatous tissue was found in two of our cases. The angiosarcomas are characterized by extreme cellularity absence of large vascular spaces and by pleomorphic nuclei.

Treatment Angiomas affecting bone are essentially benign in character They are radio-sensitive lesions and cures may be effected by deep roentgenotherapy In several of our cases where exploration and curettage were performed followed by chemical or thermal cauterization the patients have been cured. Three were cured by irradiation alone In four cases the lesions recurred following local excision. Three of these were subsequently cured by radical surgery The fourth case in the os calcis and a fifth in the upper humerus died with pulmonary metastasis Local



FIG. 461. Roentgenogram showing another view of the lesion shown in Figure 460

surgical removal or deep roentgenotherapy is indicated for the benign growths. Radical surgery is recommended for the rare malignant cases.

MYOSARCOMA

A myosarcoma originated in the voluntary muscles in a white female, aged 29, who had had recurrent swelling following an injury to the lower left femur four years previously The swelling was removed by

local operation in March, 1917 and the bone which was slightly involved was scraped. A sinus persisted after the operation and in the sinus a second tumor formed. This was excised in May 1918 and had the appearance of an organized blood clot. A fungus-like growth again appeared in the wound and in June, 1918 the leg was amputated. The gross specimen showed a periosteal tumor extensively invading the underlying cancellous bone in the internal condyle of the femur

The patient died three years and four months after the amputation with pulmonary metastases. Because of the relationship to bone and the fibroid reaction in the granulation tissue the tumor was originally classed as a fibrospindle-cell sarcoma of the periosteum. However under the microscope, a very distinct cellular picture was found, composed of large cells with small nuclei enclosed in compartments formed by an eosin-staining reticulum. These cells when cut in a longitudinal direction had definite striations characteristic of voluntary muscle The tumor was histologically identical with the rhabdomyosarcomas of other organs (heart, tongue etc.) reported in the literature



Fig. 462. (No 44886) A lipoma occurring in the knee joint and producing an erosion of the lower end of the femur The soft part shadow and roughening of the external condyle of the femur are seen

Lipoma and Liposarcoma

A white female aged 15 had a swelling of one month's duration in the region of the knee joint. The roentgenogram showed a soft part swelling slightly eroding and roughening the internal condyle of the femur The sections showed a typical benign lipoma (Fig 462) A local operation was done but the case is too recent to report the results of treatment. Two similar cases have recently been reported by Edwin I Bartlett which were distinctly benign, although Stewart† has reported instances of malignant bone involvement of supposedly liposarcomatous nature. The cases reported by Stewart, however have a markedly different microscopic picture

Three cases of liposarcoma with bone involvement occurred among 15 cases of liposarcoma of the soft parts recorded in the laboratory One patient was a white female aged 41 who weighed 190 pounds. She gained weight rapidly after her last child was born, nine years ago. Five months previous to examination there was pain in the region of the right hip which was described as sciatica. Physiotherapy was without benefit. Three months later roentgen examination of the region was interpreted as negative A second film made one month later disclosed a large soft part shadow above the ilium with areas of ero-

Bartlett, Edwin L.: Periosteal lipoma, Arch. Surg., 21 1015 1930

† Steward, Fred. W.: Primary liposarcoma of bone Am. J Path 7 87 1931

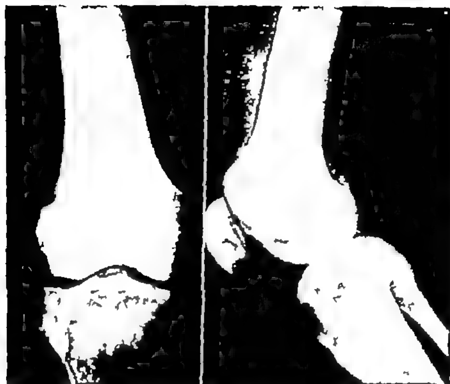


FIG. 463. Roentgenograms of a liposarcoma of the lower femur

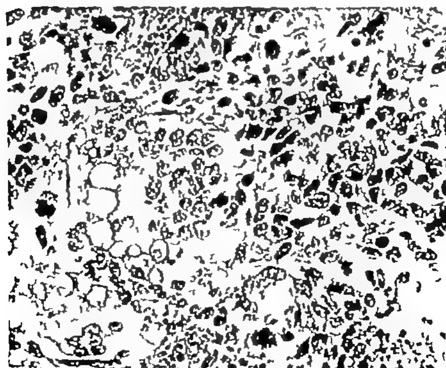


FIG. 464. Photomicrograph of the tumor shown in Figure 463



FIG. 465 Metastases to the lung in a case of liposarcoma of bone

sion along the margin of the bone (Fig 466) Examination disclosed a large palpable tumor which was lobulated and semi fluctuant and extended over the region of the right ilium and hip joint. The tumor had the consistency of a lipoma. It decreased in size after irradiation but soon afterwards resumed its growth. Biopsy disclosed loose fatty tissue with myxomatous areas and embryonic fat cells. Despite further irradiation, the patient died in May 1934, eight months after the onset of her illness, from extension of the tumor

Two liposarcomas occurred in the long bones. One in a boy of 10 years produced sclerosis in the roentgenogram (Fig 463 and 464) The other occurred in the humerus of a girl of 14 years and produced destruction of bone. The lesion was curetted under the impression of benign giant cell tumor The patient died with pulmonary metastases three months later (Fig. 465)

This small and miscellaneous group of connective tissue tumors involving the bone (non-osseous in origin and not metastatic in nature) although representing the odds and ends of a far larger collection of neoplasms primary in the bone demonstrates the variety of conditions under which neoplastic invasion of the skeleton may occur When taken in conjunction with the fibrosarcoma and neurogenic sarcoma groups, discussed in the early part of this chapter they indicate the importance of identifying pathologically the type of tumor producing the osseous change

In all the cases reported in this chapter the initial diagnosis was usually incorrect, and even after the customary pathologic examination, the tumor was in most instances incorrectly classified. The prevalent tendency is to erroneously regard these neoplasms as primarily osteogenic, or to judge them too indiscriminately as fascial sarcoma. As a result the prognosis and mode of treatment are often on an improper basis.

From the present study however it is clear that each variety of tumor warrants individual treatment. In fibrosarcoma invading bone not of the oat-cell



FIG. 466 (No 52768) Liposarcoma of the hip region eroding the ilium. The tumor occurred in a woman aged 41 and resulted fatally despite irradiation.

type, an attempt to eradicate the disease locally is justifiable, but amputation should be resorted to promptly after recurrence. In the oat-cell type, primary amputation when possible is advocated. In the neurogenic sarcoma group producing osseous involvement, primary amputation is the treatment of choice. In angiomas of the bone, local excision or irradiation may be used. For lipomas local operation is indicated, for liposarcoma irradiation and radical surgery and in rhabdomyosarcoma amputation.

SUMMARY

Two types of soft part sarcoma are prone to invade the bone by direct extension, fibrosarcoma and neurogenic sarcoma. Both of the[illegible] of malignancy cast a soft

part shadow in the roentgenogram, and produce osseous destruction, eroding the bone from without, inwardly Pathologically the fibrosarcomas may be divided into a fibrospindle cell group containing differentiated elements of the fibroblastic series and an undifferentiated spindle cell group of the "oat-shaped" cell type. In the fibrospindle cell group an attempt may be made to eradicate the disease by local operation to be followed by amputation in the event of recurrence. Permanent cures are common in this group in spite of local recurrence In the undifferentiated spindle-cell group primary amputation when possible is advocated.

In neurogenic sarcoma producing osseous involvement the prognosis is poor and even primary amputation does not often suffice to cure permanently These tumors are not radiosensitive

Angiomas, lipomas, liposarcoma and rhabdomyosarcoma invading bone are among the rarer tumors of the osseous system. The first two are benign and may be treated locally Angiomas are radiosensitive. The one patient recorded with myogenic tumor died despite amputation The liposarcomas are usually rapidly fatal

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primary tumors of the skull in the series upon which this chapter is based.

BENIGN TUMORS

Osteomas

In the membranous bones of the skull and jaws, benign osseous tumors may occur as a result of the production of new bone in ossifying fibrous tissue The more rapidly growing osteomas are predominantly fibrous tumors with small osteoid or osseous spicules embedded in proliferating connective tissue. Some of these growths are composed largely of spongy bone, while those of the more highly differentiated group are formed of dense compact bone.

Of 85 tumors classed as osteomas 30 were in the region of the upper jaws, 19 were antral or intranasal, 21 involved the lower jaws, 4 the frontal sinuses, and 2 were in traorbital. Nine occurred on the external surface of the cranium, in the region of the frontal bones one was in the mastoid region and another at the occiput. An equal number occupied the inner tables of the skull or dura, producing definite intracranial symptoms. Several of these were unattached to the skull and apparently were dural tumors.



Fig. 467 (Nos. 56028 and 56032.) Osteomas of the skull. The boy at the left was 13 years of age, with an osteoma of the frontal bone. It was successfully removed, leaving the inner table intact The patient at the right, a boy of 18 had a large osteoma at the vertex of the skull. There was a history of severe trauma in this region 14 years earlier and a tumor had been present since the age of 7 Fainting spells and convulsions had occurred during the past 2 years

Osteomas involving the membranous bones differ histologically from osteochondroma, which may occur in those areas of the skull preformed in cartilage, and from the osteophytes produced in membranous bone invaded by meningeal tumors.

The typical cranial osteoma is a benign, moundlike swelling occurring in the frontal region in a young adult. Of the 11 patients in the present series, 9 were between the ages of 18 and 33 years. The youngest was 13 years of age and the eldest 70 years. The average duration of the tumor was 18 years and 8 of the patients attributed its onset to a severe blow or fall.

Echlin has previously reported seven of

the cases in the present series, together with a group of 19 osteomas of the outer surface of the cranium collected from the literature A hard, immovable, painless swelling on the surface of the skull was the first sign noticed by all of these patients (Fig 467A, 467B) Sixteen of Echlin's 26 cases involved the frontal bone. The parietal or temporal bones were involved in eight cases and the occipital in two The growth of the tumors was slow and progressive but in several instances acceleration occurred following trauma or puberty In the late stages, intracranial symptoms such as dizziness, headaches and epileptic seizures were noted. The majority of the tumors dated back to childhood, although the patients at the time of clinical examination were adults. The usual size of the tumor at examination was between 3 and 10 cm. in diameter

The roentgen findings are characteristic (Figs. 468A and B) These show a dense mass of new bone with a smooth convex outer border and a wavy sharply demarcated base formed by the thickened or slightly depressed inner table of the skull. In the region of the outer table is a border of decreased density over the surface of the growth, which represents the growing margin of the tumor The tumor appears to be a continuation of the diploe.



FIG. 468. Roentgenograms of the osteomas shown in Figure 467 (*Top*) shows the tumor to be continuous with the diploe. Its surface is covered by a thin shell of new bone and its base is formed by the thickened and depressed inner table of the skull. In (*Bottom*) some of the new bone is arranged at right angles to the skull and differentiation from osteophytes complicating a meningeal tumor is difficult.

Osteomas of the cranial surface must be differentiated in the roentgenogram from the hyperostoses resulting from meningeal tumors invading the skull. In these lesions



Fig. 469 (No. 53574) Roentgenogram of a huge spongy osteoma of the mastoid region The patient was a child of 12.



Fig. 470 (No 45782) Roentgenogram of osteophytes occurring in a case of meningeal tumor The patient, a man aged 40 had received a blow in this region 15 years previously He lived 4 years after the appearance of intracranial symptoms. The nature of the tumor was verified at autopsy

the new bone formation shows more definitely radiating spicules which extend at right angles from both the inner and outer tables of the skull The persisting and rarefied tables of the skull can be traced through the center of the radiating osteophytes (Fig 470)

Meningeal osteophytes occur in adults, are accompanied by intracranial symptoms and such osseous changes progress rapidly This aids in distinguishing them from osteomas which have their onset in childhood, grow slowly or are stationary in size and which usually produce no intracranial manifestations. Meningeal osteophytes occur in about 10 per cent of all cases of meningeal tumor Usually symptoms of the tumor have been present for five years before the bone spicules in the overlying tables of the skull make their appearance. This duration of symptoms is approximately twice as long as the average for tumors of the meninges without bone involvement. The bones affected by osteophytes in order of frequency are frontal parietal, fronto-parietal and temporal. In some cases the bone involvement rather than the effects of the intracranial growth is first noted by the patient

In metastatic carcinoma involving the skull, both the outer and inner tables are eroded and bone destruction predominates.

Pathology The osteomas are composed of spongy or eburnated bone. The outer margin is overlaid by fibrous tissue which fuses with the surrounding periosteum, and which in the spongy osteomas is often abundant. The bony layer is continuous with the diploe or may reach the inner table. In the eburnated osteoma there is a layer of cortical bone beneath a capsule of fibrous tissue· the tumor is usually small with its base either on the outer or inner table. The larger osteomas are of the spongy type and show cancellous bone extending to the inner table

Microscopically the osteomas exhibit a layer of cortical bone underlying a zone of connective tissue. Beneath this cortical bone are trabeculae of cancellous bone varying in vascularity and in the amount of intervening fibrous tissue. The eburnated osteomas have adult quiescent lamellae of bone· the spongy osteomas, on the other hand, show cellular vascular connective tissue separating spicules of newly formed bone surrounded by more or less orderly rows of osteoblasts (Figs. 472 and 473)



Fig. 471 Massive frontoparietal osteoma in a man of 50 years. The pointed jaw suggests early acromegaly

The growth of the osteomas seems to follow the physiology of ossification in membranous bone. Normally the skull increases in thickness by deposition of bone superiosteally the latter being formed directly from preosseous connective tissue The persistence of the overlying periosteal layer and the increase of fibrous tissue in this region (Fig 474) in growing osteomas suggest that the tumor is a result of ossification proceeding from the periosteal or subperiosteal region of the skull Echlin in his study was impressed with the fact that 50 per cent of the tumors in his series arose before the eighth year of life and 75 per cent before the twelfth year He also emphasized the relatively high frequency of osteomas in the frontal or facial bones. This age incidence and distribution he related to the persistence of normal growth in the



FIG. 472. Photomicrograph of a spongy osteoma showing large amounts of fibrous tissue amid bone spicules. The tissue was removed from the patient shown in Figure 467 (*Left*)



FIG. 473. (No 55990) Photomicrograph showing the histologic characteristics of an eburnated osteoma. The lower surface is the lower margin of the inner table of the skull.

FIG. 474 (No 50026) High-power photomicrograph of the surface of a spongy osteoma, showing the formation of new bone from fibrous tissue.



FIG. 475. (No 58034) Photograph and roentgenogram of intracranial hyperostoses. The new bone is formed from the inner table. From the Pathologic Museum of Bellevue Hospital, New York.



FIG. 472. Photomicrograph of a spongy osteoma showing large amounts of fibrous tissue amid bone spicules. The tissue was removed from the patient shown in Figure 467 (*Left*)



FIG 473 (No. 55996) Photomicrograph showing the histologic characteristics of an eburnated osteoma. The lower surface is the lower margin of the inner table of the skull.

Fig. 474 (No. 50026) High-power photomicrograph of the surface of a spongy osteoma, showing the formation of new bone from fibrous tissue.

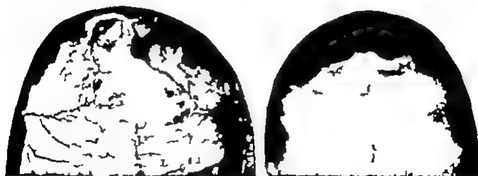


Fig. 475 (No 56034) Photograph and roentgenogram of intracranial hyperostoses. The new bone is formed from the inner table. From the Pathologic Museum of Bellevue Hospital, New York.



FIG 472. Photomicrograph of a spongy osteoma showing large amounts of fibrous tissue amid bone spicules. The tissue was removed from the patient shown in Figure 467 (*Left*)



FIG. 473. (No 55996) Photomicrograph showing the histologic characteristics of an eburnated osteoma. The lower surface is the lower margin of the inner table of the skull.

FIG. 474 (No. 50028) High-power photomicrograph of the surface of a spongy osteoma, showing the formation of new bone from fibrous tissue.

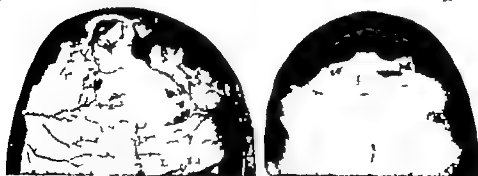


FIG. 475 (No 56034) Photograph and roentgenogram of intracranial hyperostoses. The new bone is formed from the inner table. From the Pathologic Museum of Bellevue Hospital, New York.



FIG 476 (No 47270) Roentgenogram of an osteochondroma arising from the basi-occipital bone near the attachment of the trapezius muscle. Note the irregular calcareous stippling in the lower and outer cartilaginous margin.

frontal and facial bones, which continue to increase in size through puberty after many of the other bones of the skull have ceased to grow To this latter phenomenon the increased size and more pronounced clinical features of osteomas in these regions may be attributable.

The osteomas of the skull are of special interest from the standpoint of both normal bone growth and tumor formation. The compact bone surmounting the tumor is laid down only in the presence of vascularization and resorption of underlying cancellous bone. Apparently the compact upper portion of the tumor immediately below the periosteum grows at the expense of the cancellous substance beneath. Although it is usually stated that membranous bone originates directly from fibrous tissue, it is thus seen that compact cortical bone is not formed directly but only in conjunction with the resorption of pre-existing cancellous bone. In this respect the membranous bones resemble the intracartilaginous bones, in the development of which both the resorption of calcified cartilage and the reconstruction of cancellous tissue precede the appearance of the final cortical and cancellous structures. The benign bone osteochondromas show an intervening zone of cartilage between the overlying precartilaginous connective tissue and the underlying bone. Since the final stages of cortical bone formation are similar in both membranous and intracartilaginous bone, it follows that these benign tumors, the osteochondromas and the osteomas, must proceed from the more undifferentiated or embryonic portions of the persisting connective tissues, for in the histogenesis of these lesions the entire cycle of intracartilaginous or intramembranous bone formation is repeated, rather than merely the end stages.

Treatment Osteomas of small size and composed of compact bone, which have remained stationary in size for some years may be observed by roentgenograms at intervals of 6 months to one year without treatment. Spongy osteomas or ossifying fibromas that show progressive growth should be completely excised by resecting the involved bone. The cranial defect may be closed with a tantalum plate.

Intracranial Hyperostoses and Osteochondromas

Hyperostoses of rounded or irregular contour resembling osteomas may project from the inner table of the skull in the anterior portion of the calvarium. The frontal and parietal bones are usually involved diffusely According to Yolton, this condition is observed more frequently in women than in men and is a compensation for atrophy of the brain. It is usually found only at autopsy in adults. We have observed additional cases in women with headache and manic depressive personalities. This association with functional psychosis has received emphasis in the recent literature. The compact or spongy new bone projects inwardly from the inner table without any evidence of change in the outer table (Fig 475) Mi



FIG. 477 (No. 15977) Photomicrograph of an osteochondroma of the occipital bone.



FIG. 478. Roentgenogram showing a defect in the frontoparietal region of the skull, produced by a vascular lesion. The tumor arose in the veins of the dura and the diagnosis at operation was venous aneurysm. (From Dandy W E. Arch. Surg. 17: 18.)



FIG. 479 (No. 37914) Roentgenogram of a giant-cell tumor eroding the body and wing of the sphenoid bone. The lesion occurred in a woman aged 52, who is living, but with hemiplegia, 9 years after operative removal.



FIG. 480 (No. 44198) Roentgenogram of a benign cystic defect in the skull in a male aged 26. A swelling had been present in the region since childhood. The lesion has not changed in the past three years, during which it has been under obser vation. The probable diagnosis is unresolved hematoma.

scopically the new bone formation is
ar to that in the spongy and eburnated
omas. Surgical intervention is not in
ted.

the long bones, the most common
gn tumors are osteochondromas. Of
than 300 of these recorded in this
ratory only 3 involved the skull, all in
region of the occiput Two of the pa



Fig. 481 (No 58036) Roentgenogram showing a multilocular cystic defect in the temporal region produced by a cholesteatoma.

nts were adults and the third was aged
een All three patients have remained
ll for more than five years, although one
the lesions was interpreted as probably
lignant from the roentgenogram (Fig
3) and in another a diagnosis of chon-
osarcoma was erroneously made (Fig.
7) Since the basioccipital bone is pre-
rmed in cartilage osteochondromas of
s region do not differ from those of the
ng bones. These lesions are successfully
eated by excision

ANGIOMAS (HEMANGIOMAS)

Angiomas of bone, which may be either
the cavernous or capillary type, are
und more often in the skull or spine than
the long bones. Of 12 angiomas of bone
recorded in this laboratory 5 involved the
skull. Bucy and Capp reported, among 8
cases of primary hemangioma of bone, a
cavernous angioma of the parietal bone,
operated on by Cushing In their reveiw of
the literature they found 11 angiomas of the
skull among 56 cases. The majority of these
involved the frontal or parietal bones and
occurred in adults.

In the cases recorded by Bucy and Capp
the roentgenogram showed a fine honey
combed area of rarefaction and radiating
spicules of bone overlying the tumor Two
cases in our series produced cystlike expan
sion of both tables, and little or no apparent
increase in the size of the lesion was ob-
served over a period of years. In one in
stance a congenital angioma was excised
from the scalp and skull of a girl aged 17
months. The inner table of the skull was in-
tact. In two cases previously reported by
Dandy the skull dura and brain were in-
volved. One of the lesions was described by
Dandy as a venous aneurysm arising in the
longitudinal sinus and the other as a cavern
ous angioma in the posterior cranial fossa
and extracranial occipital region (Fig 480)

Roentgen ray therapy is the preferred method of treatment in these cases, unless there are signs of intracranial pressure. The total dose varies between 1,000 and 2,000 roentgens according to the size of the lesion

This fact is borne out by the four giant cell tumors of the skull in the present series. Two of these presented in the temporal fossa, arising from the sphenoid bone, one occurred in the mastoid region and involved the auditory meatus, and the fourth devel



Fig. 482. (No. 56036) Photomicrograph showing the epithelial lining of the tumor in Figure 481

oped in the occipital region The ages of the patients at the time of the initial examination were 14, 42, 52, and 70 years. Although in three of the four cases there was a recurrence after excision, none of the patients died of tumor Excision of the lesion in the temporal fossa resulted in a cure in the youngest patient, who is reported well 20 years later The tumor in the body of the sphenoid bone (Fig 479) occurring in a white female aged 52 years, apparently caused hemiplegia four years after operation. The patient is still living with spastic paralysis nine years later The tumor in the *mastoid region* invaded the cranial cavity

Giant Cell Tumors of the Skull

A study of over 300 giant-cell tumors in various skeletal and extraskeletal locations indicates that there is an intimate relation between pathologic giant-cell proliferation and the physiologic processes of absorption in intracartilaginous bone. With the exception of the giant-cell epulis, which forms around the roots of deciduous teeth, giant cell tumors are *usually confined to the intracartilaginous* bones or to the sesamoid bones in the tendon sheaths derived from fibro-cartilage. In the skull therefore, they should be restricted to those regions which *develop from the chondrocranium.*

and at the third operation a portion was removed from the brain substance; the patient, however, is free of symptoms 12 years later.

Roentgenographically giant-cell tumors of the skull produce a sharply demarcated area of bone destruction. Microscopically blood spaces surrounded by giant-cells. It is possible that this lesion was a posttraumatic vascular defect *with giant-cell osteoclasts* (diploic hematoma). Such a histologic picture may also be seen in inflammatory lesions of the diploe (Fig. 485). They are best treated by excision.



FIG. 483. (No. 48488.) Roentgenogram of osteomyelitis of the parietal bone. Note the small, dense, rounded sequestrum at the lower posterior portion of the lesion.

they do not differ from giant-cell tumors of the long bones. We have been able to find only two cases of giant-cell tumors of the *skull in the literature*, one reported by Troell, the other by Fraser.

Troell's patient was a man of 20, and the tumor had supposedly been present from birth. At the age of 3 it was excised and reported as giant-cell sarcoma. At the age of 20 it was about the size of an adult fist and was encased in a shell of bone. The tissue removed at this time showed only a bone cyst containing blood, cholesterin, plasma cells and lymphocytes. This case demonstrates that a healing giant-cell tumor may be converted into a benign bone cyst. Fraser's case, occurring in a man of 42 and of 5 months duration, *is of interest because* of its location in *membranous* bone. The tumor was removed from the left half of the frontal bone following deep roentgenotherapy. Microscopic examination showed

Cystic Lesions of the Skull

Isolated defects in the cranial bones may be observed in roentgenograms of the skull in young adults following the discovery of a mass overlying a membranous bone. There may be a history of trauma or infection, or the mass may date from early childhood. The lesions are practically asymptomatic. Such defects are often classed as bone cysts clinically and microscopically; the cyst wall and contents are diagnosed as xanthomas or cholesteatomas by pathologists. Some are deploic abscesses or hematomas, as stated above.

Cholesteatomas. Cushing restricts the term cholesteatoma to epithelial lined cysts which may arise in the leptomeninges at *the base of the skull*, in the infundibula or cerebellar regions, or in the diploe, usually in the region of the petrous or squamous portion of the temporal bone. They may also occur in the walls of the ventricles,



FIG 484 (No 54286) Roentgenograms of the skull, anteroposterior and lateral, showing a Brodie's abscess in the diploe. The defect followed a pelvic infection 6 weeks previously

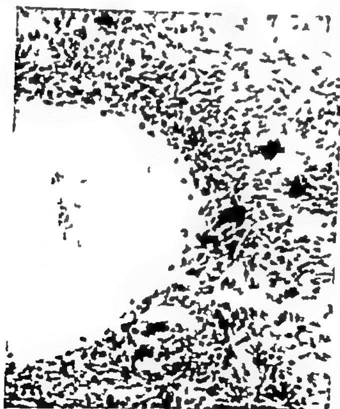


FIG. 485 (No. 54286) Healing diploic abscess photomicrograph of tissue removed at operation in case shown in Figure 484. Vascular areas such as this, surrounded by foreign-body giant cells, were numerous. Other areas showed lymphocytes, foam cells and blood pigment, suggesting a diagnosis of xanthoma.



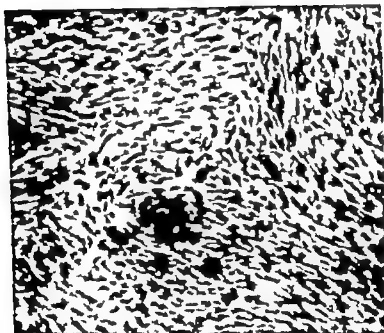


FIG. 486 (No 31267) Fibrosarcoma of the parietal bone. The roentgenogram shows a circular defect. The photomicrograph shows a low-grade fibrosarcoma, probably arising from the outer layers of the periosteum The patient was a white female aged 34, who had first noticed a painful mass accompanied by headache two and a half months prior to operation. She died five years after excision of the tumor from intracranial extension.



FIG. 487 Diploic hematoma which responded to roentgenotherapy

Pathologically dermal and epidermal types are recognized, the dermal types enclosing epithelium and hair the epidermal type having a transitional squamous-cell lining. Cruveilhier in 1829 described the dermoid type under the name pearly tumor and Johannes Mueller in 1838 described the epidermal form, reporting three cases, one of which involved the diploe of the skull. He introduced the term cholesteatoma because of the cholesterin crystals found in the cyst contents.

Cholesteatomas involving the diploe are less common than those found in the leptomeninges. They produce clearly demarcated areas of bone resorption which may be multilocular eroding the inner table and thinning the outer table. The margin of the growth has a wavy or lobulated outline. The lesions are most commonly found in the temporal bone (Figs. 481, 482) but Cushing was able to collect eight cases, including a case of his own, of epidermal cysts of the diploe three of which were in the frontal, two in the parietal, and three in the occipital bone.

Microscopically the cysts are seen to be contained within a fibrous and epithelial wall under a thin external table of bone with a few adherent plaques representing the remains of the internal table. The cyst contents may be rich in cholesterin crystals. The epithelial lining usually shows five or more rows of transitional epithelium resting upon a wall of vascular connective tissue. The tumors apparently arise from epithelial implants carried into the bone during embryonic development,

SPURIOUS CHOLESTEATOMAS

Temporal cholesteatoma related to chronic ostitis media is a special variety It involves the cavities of the middle ear and the adjacent mastoid cells. In this process the normal lining cells are replaced by squamous epithelium, which deposits cheesy infected keratinized material into an expanding cavity The squamous cells may arise by metaplasia from the middle ear lining cells or grow in through a ruptured ear drum, from the external auditory meatus. Both true and spurious cholesteatomas are best treated by thorough curettage.

Infectious and Traumatic Defects (Diploic Abscess and Diploic Hematoma) Typical osteomyelitis of the cranial bones, with irregular new bone production, bone destruction and small rounded sequestra is easily recognized in the roentgenogram (Fig. 483) Such lesions are usually secondary to infections of the scalp sinusitis, mastoiditis or brain abscess. Syphilitic osteitis is not uncommon in the frontal and parietal bones. Diagnosis is made serologically Confusion with primary tumors of the skull, however may be occasioned by solitary defects of inflammatory origin (Fig 484) Such areas of bone erosion in the present series have been observed in 12 instances several weeks after the occurrence of laryngitis, salpingitis, phlebitis or septicemia. A palpable fluctuant tumor may be found overlying the osseous defect and aspiration or incision yields fluid mixed with granulation tissue or granulation tis-

alone. Microscopic examination fails
veal an epithelial lining. The granula
tissue shows plasma cells, giant cells,
d laden phagocytes and other wander
cells. Because of involvement of the
e the tissue may be quite vascular

cases, both of which have remained well following curettage.

Cranial Bone Cyst In rare instances osteitis fibrosa cystica accompanied by areas simulating giant-cell tumor may affect the membranous bones without dem



FIG. 488. (No 45934) Osteolytic sarcoma of the parietal-occipital region. The patient was a white female aged 22, who had noticed a mass accompanied by headaches three years previously The tumor at the time of examination was about the size of an orange The roentgenogram shows an irregular area of bone destruction at the junction of the parietal and occipital bones.

ch granulation tissue is nonspecific and,
hough sometimes interpreted as xan
oma or Schüller-Christian's disease, as
eitis fibrosa, or even giant-cell tumor it
the result of an infection similar to
odie's abscess of the long bones. We pre
the term diploic abscess.

Cranialosseus defects without an epithe-
l lining and containing granulation tissue
termingled with blood and blood pig
ent may result from hemorrhage follow
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m sclerotic bone both tables of the skull
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ported such hematomas of the diploe
nder the diagnosis of encapsulated cephal
ematoma. We have observed two similar

onstrable involvement of the remainder of the skeleton. Chorobski and Davis have attempted to collect such cases from the literature. The one case observed by these authors personally showed not a solitary defect but multiple recurring lesions of the cranium. Studies of the blood calcium and blood phosphorus were not made In our own series of solitary bone cysts, approximately 200 cases, we have never observed such a solitary lesion in the membranous bones of the skull.

PRIMARY SARCOMA OF THE CRANIAL BONES

Sarcoma arising from the cranial bones is rare. In a series of more than 700 cases of



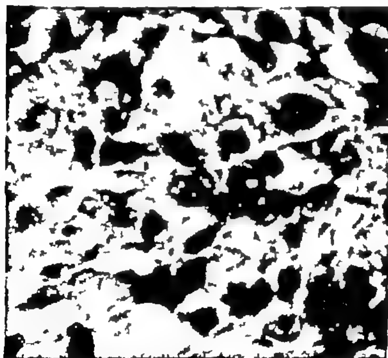


FIG. 489 (No. 45934) Low-power and high-power photomicrographs of the tumor shown in Figure 488. Suggesting a histologic variant of giant-cell tumor The high-power photomicrograph shows malignant cells in the stroma. The roentgenogram and the location in membranous bone were against the diagnosis of benign giant-cell tumor The patient died fifteen months after excision of the tumor with metastasis to the lung, confirming the diagnosis of osteolytic sarcoma.



FIG. 490 (No 49630) Photograph of patient and roentgenogram of an osteogenic sarcoma arising at the junction of the parietal and occipital bones.



FIG. 491 (No. 46970) Osteolytic osteogenic sarcoma arising in the occipital-parietal region. This is the most common site for osteogenic sarcoma of the skull.

primary bone sarcoma, the upper and lower jaw were involved in 28 cases, but the cranial bones in only 12. With one exception the patients were children or young adults. Practically all of the cases occurred in the vault of the skull in the region of the parietal bone sometimes at its junction with the occipital or temporal. Eight of the 12 cases were varieties of osteogenic sarcoma, sclerosing, osteolytic and chondral forms. One was a fibrosarcoma apparently arising from the outer layers of the periosteum and three were Ewing's sarcoma.

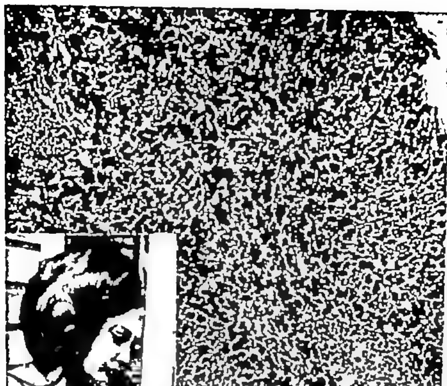


Fig. 492. (No. 27325) Sclerosing osteogenic sarcoma arising from the posterior parietal region in a girl of 1[illegible]. The inset in the lower left hand corner shows the appearance of the patient. She had noticed swelling and pain in this region for 8 months. Death occurred [illegible] months after excision of the tumor. Deep roentgen and radium therapy were without benefit.



Fig. 493. (No. 36038) Photomicrograph of a chondrosarcoma arising at the base of the anterior fossa of the skull. (Drs. Stevenson and Symmers, Bellevue Hospital, New York.)

Osteogenic Sarcoma

Osteogenic sarcoma of the skull may be of the sclerosing or chondrosarcoma type The osteolytic variety occurred twice in the present series (Fig 491) The discovery of the growth may be preceded by head aches. The tumor increases rapidly in size but in general the duration prior to exam ination is longer in the skull than in other regions. All forms of osteogenic sarcoma in the present series showed a tendency to destroy the tables of the skull as well as to produce a periosteal reaction and to in vade the overlying soft parts (Figs. 490 and 494) Despite this destruction of bone, all but one of the patients in the present series died of metastases rather than of intra cranial extension. In one patient there were metastases to the spine and ilium in the terminal stages of the disease. The roent gen diagnosis is based upon bone destruc tion in the tables and diploe the periosteal reaction in the adjacent areas, and, in the late stages, extension of the tumor into the soft parts. In all instances, however the nature of the lesion can be determined adequately only by biopsy Neither excision nor irradiation proved beneficial in the present series. Resection of the involved bone is the treatment of choice if the lesion is diag nosed in time

Microscopically the predominant feature may be new bone formation with irregular spicules surrounded by proliferation of malignant osteoblasts. This is the sclerosing form (Fig 492) In the osteolytic tumors large malignant osteoblasts and small giant cells of the epulis type are predominant (Fig 489) Adult and fetal cartilage may occur in osteogenic sarcoma at the occiput.



Fig. 494 (No 51502) Osteolytic sarcoma developing in Paget s disease of the skull.

A case of typical chondrosarcoma (Fig 493) involving the base of the skull was seen on the pathologic service of Bellevue Hospital and is included here through the courtesy of Dr Louis Stevenson and Dr Douglas Symmers.

The patient was a white female aged 64 who had noticed progressive exophthalmos for a period of [illegible] years. There was loss of vision in the left eye with dimness of vision on the right and bilateral proptosis. The sense of smell was lost and breathing through the nose was difficult Five months prior to operation convulsions first occurred. The roentgenogram showed destruction of the nasal portion of the right orbit extending into the ethmoid cells and the sphenoid bone Numerous calci fied deposits were seen in the brain tissue and anterior fossa near the *midline*.

On May 22, 1930 operation was performed for a tumor at the base of the anterior fossa, eroding through the palate and extending into the sinuses and pharynx. Excision was made above the eyebrows and the frontal bones

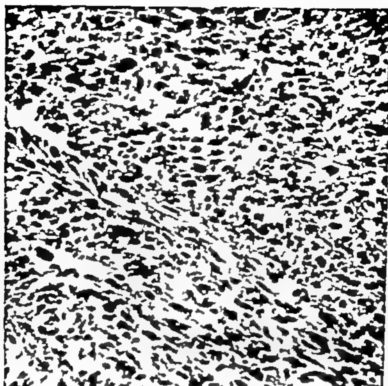


Fig. 495 Photomicrograph of sarcoma shown in Figure 494

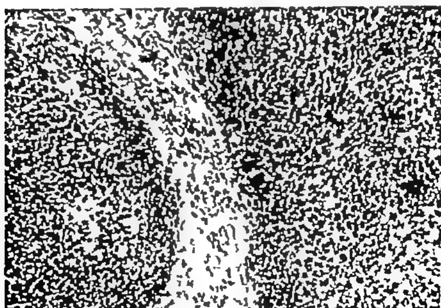


Fig. 496. (No. 49672) Photomicrograph of Ewing's sarcoma arising in the occipital bone



Fig. 497 Spheno-occipital chordoma of the pseudo-alveolar type

rongeured away down to the roof of the or bits. The frontal sinuses were curetted. The bone at the back of the anterior fossa was soft and necrotic and adhered to the overlying tumor The frontal lobes above the tumor tissue were thin and degenerated. The tumor was shiny and lobulated, invading the bone but not the brain substance The ethmoidal and sphenoidal sinuses were exposed at the removal of the tumor

The patient died postoperatively At autopsy a portion of the tumor tissue left behind at operation was found attached to the region of the pituitary and the left middle fossa, bulging like a mushroom from the bone beneath. It was about the size of a lemon. The tumor was lobulated and pearly white, with translucent cartilaginous areas. It was firmly attached to the body of the sphenoid, obliterating the sella turcica. Its microscopic features are shown in Fig 493. Anteriorly the mass removed at operation had eroded the frontal sinuses, the bony structures of the nose the walls of both orbits and the roof of the mouth.

Ewing's Sarcoma

There were three cases of Ewing's sarcoma in our series, two involving the mastoid process and one primary in the frontal bone Two of the cases were in children and one in a young adult, aged 22. The two tumors in the mastoid region (Fig. 496) were excised, and as far as could be determined both patients died (currence rather than metastases The tumor which involved the frontal destroyed practically the entire anteri of the vault. The upper ribs, clavicl left tib a were also involved in this Despite the immense size of the



Fig 498 (No 36943) Malig vascular tumor probably a form of giosarcoma originally reported as atypical chordoma. The tumor inv the occipital bone.

tumor it is possible that the lesion skull was a metastasis from a primar in the tibia These tumors of the sk be treated palliatively by irradiatic cures have not been effected.

CHORDOMA

Chordoma is a rare malignant ne found at either extreme of the spi and occasionally elsewhere in the column. It is generally accepted as o ing from embryonic remnants of th chord. Although in the adult remn the notochord persist in the interv discs in the form of the nucleus pu the majority of chordomas arise e the spheno-occipital or sacrococcy gion They have also been reporte cervical spine and rarely in the d lumbar region. Mabrey collected 1 viously recorded cases in 1935

Coenen found 36 cases in the sp



FIG. 499 (No 36943) Photomicrograph of tumor shown in Figure 498

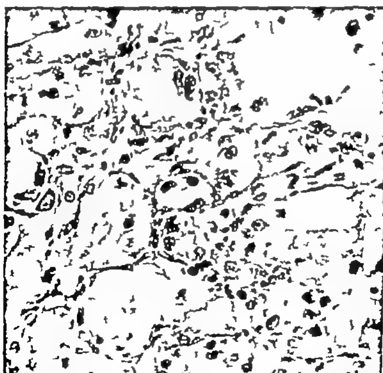


FIG. 500 (No 36943) High-power photomicrograph of the tumor shown in Figure 499 The tumor cells are extremely variable in size and are undergoing vacuolization.

23

Tumors of the Jaws

DENTAL TUMORS
SARCOMA OF THE JAW
MALIGNANT EPITHELIAL TUMORS

Tumors of the jaws are epithelial, osseous or dental in origin. The epithelial tumors, like those of the skin, are epidermal or basal-cell in type arising from the neighboring mucous membranes or their appendages and invading the jaws by direct extension. The malignant osseous tumors (including osteogenic and Ewing's sarcoma) resemble those of the long bones. The benign bone tumors show features peculiar to this region. The osteomas and ossifying fibromas show a mode of ossification characteristic of membranous bone. The giant-cell tumors may be central or peripheral. The peripheral giant-cell tumors (epulides) are related in their origin to the eruption of the permanent teeth.

The dental tumors are usually cystic in character and contain epithelial elements. In their histogenesis they are related to the enamel organ which is derived from the oral ectoderm. The classification and incidence of these tumors of the jaws as recorded in our series is given in Table 85.

The teeth are ectodermal derivatives embedded in the osseous substance of the upper and lower jaws. The body of the tooth is composed of dentine and the crown of enamel. The dentine is ossified mesoderm condensed from the neighboring dermis which forms the dental papillae. The enamel is a secretion of epithelial cells derived from the ectoderm and corresponds to elements of the exoskeleton found in other vertebrates. These epithelial cells form a dental lamina behind the lips, from which twenty enamel buds normally arise during the third month of embryonic life to

TABLE 85

Type	Cases	Cases
Dental and Benign Osseous Tumors		265
Radicular cysts	57	
Follicular or dentigerous cysts	12	
Adamantinomas	45	
Odontomas	5	
Giant-cell epulis	51	
Central giant-cell tumors	25	
Osteomas and ossifying fibromas	70	
Malignant Osseous Tumors		44
Osteogenic sarcoma		
Sclerosing	10	
Chondral	7	
Ewing's sarcoma	19	
Tumors with skeletal and jaw involvement	8	
Epithelial Tumors		14
Epidermal cancer exclusive of 75 antral tumors	8	
Adenocystic basal-cell carcinoma	2	
Metastatic carcinoma	3	
Aberrant parotid	1	
Total		323

form the future crowns of the milk teeth (Fig. 502)

Both the dental lamina and its derivative the enamel organ may give rise to persistent strands of undifferentiated basal cells which may take part in tumor formation. From these cells dental root cysts, follicular or dentigerous cysts, and adamantinomas may arise. Remnants of the down-growing basal cells nearest the primitive mucous membrane (known as epithelial débris of Malassez) under stimulation of root granulomas differentiate to form a lining membrane of squamous cells forming dental root cysts. The cell layers of the enamel organ surrounding a degenerating stellate reticulum (Fig 501) may expand about the non erupted tooth to form a follicular or dentigerous cyst. More primitive elements of the enamel bud may proliferate and differentiating in several directions produce islands of enamelblasts, squamous cells and basal cells, a mixture of epithelial elements characteristic of adamantinomas.

The enamel buds overlie the dental papillae. In these mesodermal papillae the dentine is formed. The unossified portion of the dentine forms the tooth pulp below and above forms the dental sac. The dental sac in the region of the roots of the teeth forms a membrane which ossifies to produce cementum and acts jointly as a pericementum for the roots of the teeth and as periosteum for the alveolar processes of the jaw (Fig. 502) Proliferation of these mesodermal elements is found in odontomas.

The eruption of the milk teeth is complete in 18 months, and the permanent teeth in 18 years. Before the eruption of the permanent teeth, giant-cell odontoclasts appear in the pericementum, which loosen the temporary structures. These cells may give rise to giant-cell tumors of the alveolar ridge known as giant-cell epulides.

DENTAL TUMORS

The dental tumors are characterized by their tendency to occur in young adults, by their relatively benign character and slow growth, by the production of central cystic expansions within the jaws and by their tendency to recur if not completely removed. Pathologically they are divisible into three major groups (1) the cystic epi



FIG. 501 Diagram illustrating the invagination of the enamel bud from the ectoderm of the dental lamina The two concentric domes of epithelium are separated by a stellate reticulum and attached above to the oral ectoderm by a narrow gubernaculum. From the lower and inner dome of epithelium the enamel develops. This layer supposedly gives rise to adamantinomas. The outer dome and the gubernaculum give rise to epithelial debris which is instrumental in forming the cystic dental tumors of the jaw

thelial tumors, (2) tumors characterized by giant-cell proliferation, and (3) benign new growths composed of compact cellular fibrous tissue which shows a tendency to ossify

No classification for epithelial cysts of the jaws has received general acceptance. Cysts lined by squamous cells occur in connection with root granulomas and are known as

radicular or dental root cysts. These tumors are relatively common. A rarer group with the same type of epithelial lining bears a relationship to nonerupted teeth. These are variously known as follicular or dentigerous cysts. A third group the adamantinomas, may form cystic or solid tumors with definitely malignant tendencies. The predominant tissue is composed of undifferentiated basal cells which may differentiate into enamel or squamous cells. A rare form of tumor the odontoma, is sometimes classed as a follicular cyst, sometimes as a subvariety of adamantinoma.

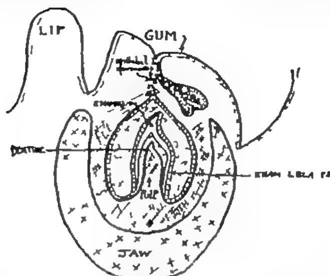


Fig. 502. Diagram illustrating the relationships of the enamel organ and dentine to the jaw and oral epithelium of a human fetus of 5 months.



Fig. 503 (No 35946) Roentgenogram of a monolocular radicular cyst. Note the sharply demarcated outline of the cyst wall.

Tumors characterized by giant-cell proliferation may occur centrally within the jaws or peripherally along the alveolar margins. The latter are usually classed as epulides. The ossifying fibrous tumors are usually subperiosteal in origin, but their tendency to embed themselves within the jaws and to be composed histologically of very cellular connective tissue, has led to



Fig. 504 (No. 40810) Roentgenogram of a polycystic radicular cyst persisting after the extraction of infected teeth. The cyst lining was not removed.

the term central fibroma and central fibrosarcoma of the jaws, in the older literature More recently they have been regarded as identical in their pathology with solitary fibrous dysplasia of the long bones.

In the roentgenogram a central area of rarefaction with well-defined outlines extends in semicircular fashion about the root of the devitalized tooth. This outline distinguishes the cyst from the ordinary root





Fig 505 (No 39578) Low-power and high power photomicrographs showing the epithelial lining of a radicular cyst and its relation to granulation tissue

Radicular or Dental-Root Cysts. These fairly common dental tumors are characterized by the formation of a cyst about the root of a devitalized tooth as a sequence to chronic inflammatory changes. While radicular cysts occur at all ages, the 57 cases in our series occurred chiefly in young adults. The lower jaw is more often the site of these growths than the upper and the molars and bicuspids are more commonly involved than the region of the anterior teeth. Rarely a cyst may be discovered at the site of a tooth which has been previously extracted without removal of the attached cyst. In their earliest stages these lesions produce no symptoms, but expand slowly and painlessly at the expense of the osseous substance of the jaw In the maxilla the antrum is encroached upon. Occasionally a sinus tract is formed and infected material drains into the mouth. The larger cysts produce visible expansion or swelling, which is firm to palpation and in advanced cases may give a parchment like crepitation.

granuloma with hazy margins (Figs 503 and 506) The expansion of the cyst about the apex rather than the crown of the tooth, and the absence of a nonerupted tooth,



Fig. 506 Roentgenogram of radicular cyst with an adjacent nonerupted molar

distinguish these growths from dentigerous or follicular cysts. The cavity in the roentgenogram is usually monolocular but rarely multiple cysts forming around several neighboring teeth may give the impression of multilocularity Upon exploration a definite fibrous wall is encountered, with a smooth epithelial lining enclosing yellow or brownish fluid. Rarely the cyst granulomas to be converted into radicular cysts are against the view that adult mucous membrane gives origin to the epithelial lining

The treatment of radicular cysts consists in extraction of the tooth, opening of the cavity and evacuation of its contents, including removal of the epithelial lining of the cyst wall The material removed



FIG. 507 (Nos. 44050 and 51374) Roentgenograms of follicular or dentigerous cysts. In the figure on the left the nonerupted tooth is seen to one side and at the bottom of the cavity in the lower jaw (previously published by Kegel)

contents may be mucoid or purulent. In the latter cases a sinus tract is usually present. Under the microscope a lining of transitional epithelium is seen, which may vary in thickness from one to many cell layers (Fig 505)

While in their origin these radicular cysts are related to dental granulomas, opinion is divided concerning the source of the epithelial lining which surrounds the gradually expanding cavity Strands of epithelium in the ordinary root granuloma are not uncommon. Whether these strands proceed inwardly from the surface of the mature mucous membrane surrounding the tooth or originate from the fetal epithelial remains of the invaginating enamel buds (epithelial débris of Malassez) is in dispute. The weight of evidence is in favor of the latter interpretation. The absence of a sinus tract and the failure of the majority of root should always be subjected to pathologic examination. With such treatment recurrences are practically unknown

Follicular or Dentigerous Cysts. Follicular cysts arise from the epithelium of the enamel organ during the development of the teeth. They are relatively rare. They are characterized by the presence of a nonerupted tooth, the cyst expanding about the crown of the tooth rather than about the root. Because of their relationship to the developing teeth, they are usually found in young individuals. In the 12 cases in our series, the majority of patients were under the age of 15 One patient was 25 years old and another 32. These lesions are most frequently found in the region of the third molar There are no striking clinical signs except failure of the tooth to erupt and expansion of the jaw at the tumor site.

Several varieties of follicular cysts are

described, which are rare and clinically un important. A cyst in which the tooth is absent because of early degeneration of the enamel organ is termed a simple follicular cyst. These cysts are found at the site of the third molar and microscopically are indistinguishable from radicular cysts. Cysts occurring at the site of a supernumerary fourth molar are sometimes termed paradental cysts. The so-called odontoma is sometimes classed as a form of follicular cyst. It is essentially a subvariety of adamantinoma.

The most common variety of follicular cyst is the so-called dentigerous cyst. This is formed in the later stages of development of the enamel organ and shows in the roentgenogram a nonerupted tooth within a monolocular cyst (Figs. 507 and 508) The tooth is pushed away from the gum by the growth of the cyst, which expands about the crown. Various stages of development from a poorly formed dense area of enamel to a complete tooth are found usually a well formed tooth is present.

Exploration reveals a fibrous cyst wall lined by stratified epithelium containing a serous or amber-colored fluid. The epithelial lining is connected at the neck of the tooth with the dental cuticle, which is continuous with the lining membrane. The lining of the cyst under the microscope is usually transitional epithelium, indistinguishable from that of the radicular cysts. With infection it may be replaced by granulation or fibrous tissue Remnants of adamantine



FIG 508 (No 48734) Roentgenogram of a polycystic lesion combining the features of dentigerous cyst and adamantinoma. Two teeth are contained in the cavities which have expanded the lower jaw The one near the symphysis resembles the cyst shown in Figure 507





FIG. 509 (Nos. 36356 and 40822) Roentgenograms of adamantinomas of the lower jaw (*Left*) The cavity has the typical honeycombed appearance (*Right*) Multilocular cavities without expansion of the jaw are seen.

epithelium (undifferentiated enamelblasts) may be found in the lining of cysts containing one or more nonerupted teeth (Fig 508) Opinion is divided concerning the classification of such cysts. By some they are regarded as dentigerous cysts which have undergone conversion into adamantinoma by others as cystic adamantinomas.



Fig 510 (Nos. 44222 and 42439) Photomicrographs of adamantinomas. (*Left*) Shows an island of squamous cells surrounded by a rim of compact basal cells (*Right*) Shows the differentiation of enamelblasts in the tumor (From Kegel Arch. Surg 25: 498.)

The follicular cysts, like the dental root cysts, are best treated by complete evacuation of the contents, including the lining membrane and the nonerupted tooth. Recurrence is rare except in those cases which may be classed as cystic adamantinomas with nonerupted teeth

Adamantine Epithelioma. The adamantinomas may be looked upon as a neoplastic and potentially malignant homologue of follicular cysts. These tumors bear a definite relation to the enamel organ, as was first pointed out by Broca in 1868 The tumors occur most commonly in young adults, the major age incidence being between 10 and 35 years, an age distribution similar to follicular cysts. They are more common in the lower than the upper jaw in the ratio of 36 to 7 in the present series. In the lower jaw the molar region is the predominant site the tumors in the upper jaw involve the antrum from the region of the canines to the molars. The relative incidence of adamantinomas in the colored race is high. Growth is extremely slow progressing over periods of 5 to 50 years. Facial deformity rather than pain usually brings the patient to the physician. An oval swelling extending outward rather than obstructing the oral cavity is found. The shell of bone surrounding the tumor may be thick or thin, depending on the size of the growth. Rarely a sinus opens into the oral cavity and drains fluid or purulent material.

One of the striking symptoms of adamantinoma is a loose tooth, which is a common symptom of malignancy in either the upper or lower jaw and one which too often is treated without adequate investigation with the possibilities of a malignant condition in mind.

Roentgenologically the adamantinoma is a monocystic or polycystic central tumor of sharp outline (Fig. 509) without an overlying periosteal reaction such as is seen in sarcoma and without the worn eroded edge of cancer or the association with new bone production seen in osteomyelitis. The polycystic tumor with a honeycombed appearance is to be differentiated from the trabeculated giant-cell tumor or the mono-

cystic radicular or follicular cyst. Such differentiation in the roentgenogram is by no means absolute as occasionally any of the central tumors of the jaw may produce a similar picture Conversely an adamantinoma may form a *monolocular cyst in the* roentgenogram, resembling a radicular cyst, and the presence of a tooth in such a cyst may mimic a follicular cyst.

The tumors may be solid or cystic, and the cystic areas may occasionally be lined by stratified squamous epithelium resembling the follicular cyst and may contain unerupted teeth. The microscopic structure of adamantinoma is extremely variable The tumor arises from undifferentiated basal cells which may approach either squamous epithelium or enamel epithelium in the differentiated state (Fig 510) The islands of basal cells may resemble adenocystic basal-cell cancer or in more characteristic fashion may surround an area of stellate reticulum (Fig 511) Although as a rule the proliferation of epithelial elements predominates, in rare instances large amounts of embryonic stroma resembling primitive mesenchyme are present. Such mesenchymal tumors, combining in their structure both the histologic elements of the dentine and the epithelial elements of the enamel organ, are generally regarded as *odontomas, and may contain varying* amounts of calcareous material (Fig 512)



Fig 511 (No 14752) Photomicrograph of an adamantinoma showing the formation of a stellate reticulum within the tumor tissue

Kegel, who studied the adamantinomas recorded in this laboratory has come to the conclusion that they arise from the cells of the enamel organ rather than the paradental *débris* of Malassez. That is, the inner epithelial layer of the enamel organ (Fig 501) is regarded as the site of origin for these growths *rather than* the outer and upper layer which gives rise to the so-called epithelial débris. Their prevalence at the site of the third molar and *in* colored patients suggests a relationship to aberrant tooth germs at the angle of the jaw Moreover in several cases *in this series* the nonappearance of a tooth at the tumor site or the occurrence of nonerupted teeth within the tumor mass indicated a relationship *to* the benign follicular cysts which have their

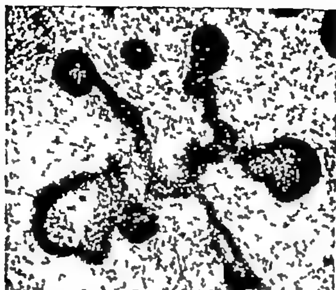


Fig. 512. (No. 23935) Photomicrograph of an adamantinoma in which the epithelial elements are surrounded by large amounts of mesenchyme or primitive dentine. This type of tumor is referred to by some authors as "soft odontoma."

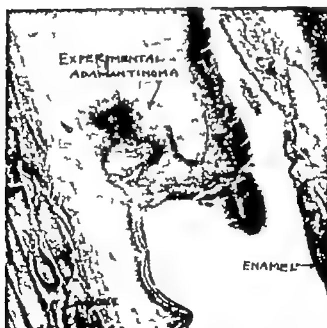


Fig. 513. Photomicrograph showing the distortion and irregularity in the enamel epithelium in a rachitic pig. The animal was kept on a rickets-producing diet for 9 months. Note the epithelial nests budding off into the region of the dental sac. (Dr H Klein, School of Hygiene, Johns Hopkins University Baltimore Md.)

origin in an abnormality of development in the enamel organ.

Rickets, very common in colored patients, may play an etiologic rôle in the occurrence of adamantinomas. With the dietary deficiency in this disease marked defects in the development of the tooth germs and particularly of the enamel have been

manent cure averages about 80 per cen the present series although the majority the patients living had one or more rec rences. In the recurrent cases the inter between the first and second operation between 5 and 11 years. Radical resect is justified in recurrent cases. Metastasi extremely rare (it occurred once in this



FIG. 514. (No. 51883) Photomicrograph of an adamantinoma occurring in the hypophyseal stalk. In the past year the patient had increasing headaches, polyuria and a gain in weight of 25 pounds. Both squamous and columnar epithelium are shown.

unquestionably established. In rickets, the enamelblastic layer of the enamel organ becomes irregular and islands of these cells bud off and become isolated. The occurrence of such irregularities in the enamel organ with resultant isolation of enamel pearls and small tumors is demonstrated experimentally by the feeding of rickets-producing diets to pigs during the active period of development of the teeth and gums (Fig 513)

The treatment of choice is curettage followed by cauterization. The disease shows a marked tendency to recur and the recurrent tumors are difficult to eradicate. In such cases, resection, if not too mutilating, should be practiced. The adamantinoma is relatively radioresistant, and irradiation osteitis of the jaws is prone to complicate adequate dosage The prognosis for a per

ries) death usually being due to di extension to the skull and brain. Thoma reported a case of Simmons of Bo with metastases to the lymph nodes at bifurcation of the carotid, microscopic verified. Resection of the mandible ar radical neck dissection were perforn The patient was well eight years l without signs of recurrence.

Aberrant Adamantinomas. Adaman mas have been recorded in the ovary tibia and the hypophyseal duct. Thos the ovary are undoubtedly teratomatou origin. Three cases of adamantinoma of lower tibia have been reported. These l been reviewed by Gray whose case been recorded in this laboratory (516)

Adamantinoma is one of the outstan histologic types of solid tumor occurri

the hypophyseal duct. Of 10 tumors in the hypophyseal stalk recorded in this laboratory 6 were microscopically diagnosed ad amantinoma (Fig 514) These tumors occur characteristically above the sella turcica and may invade the hypophysis, producing endocrine symptoms, of which

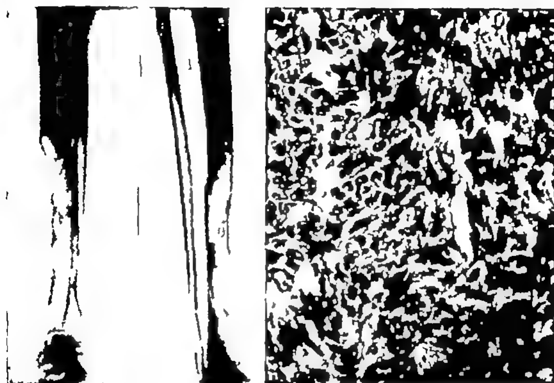


FIG. 515 (No 58380) Roentgenogram and photomicrograph of a cellular adamantinoma of the tibia.

the commonest is the syndrome of dystrophia adiposogenitalis. According to Duffy who reviews the embryologic studies of Erdheim, the pituitary duct, which forms from the ectoderm of the oral cavity gives rise to cell rests of the epidermal type from which adamantinomas may arise. He distinguishes these tumors from the cysts of Rathke s pouch, which develop from the cleft between the anterior and posterior lobes and which are lined by ciliated epithelium. The occurrence of adamantinomas in the hypophyseal stalk and in the tibia is against the specificity of the enamel organ as a source for these growths.

Odontomas. Odontomas are mixed tumors combining derivatives of the enamel epithelium and of the connective tissues of the dental papilla. Epithelial strands like those found in adamantinomas occur also in odontomas, but are overshadowed in quantity by mesenchymal elements. In the so-called immature or soft odontomas, large amounts of undifferentiated connective tissue with varying amounts of myxomatous change are combined with epithelium of the adamantinoma type (Fig. 512) Clinically these tumors behave like adamantinomas and represent a transitional group which merges with the more frequent and benign, hard odontomas. Thorough curettage and cauterization is the treatment of choice.

The hard or differentiated odontomas are about twice as frequent in occurrence as adamantinomas of all types.* They are

* This incidence is based on cases recorded in the New York Institute of Clinical Oral Pathology



FIG. 516. (No 51660) Roentgenogram and photomicrograph of adamantinoma of the tibia. (Dr J W Gray)

FIG. 517 Roentgenogram and photomicrograph of adamantinoma of the tibia

found usually in the lower jaw of young individuals, at the site of an unerupted tooth. They may arise from the imperfectly differentiated elements replacing the un-



FIG. 518. (No 54994) Roentgenograms of a composite odontoma occurring in the mandible of a boy of 14 years. Above the unerupted molar is a calcareous mass in which several small, poorly developed teeth are visible A well-demarcated area is produced in the lower jaw which contains tumor tissue of varying density

erupted tooth (simple odontoma) or from accessory tooth germs adjoining the unerupted tooth (composite odontoma) In the roentgenogram, irregular dense calcified masses are seen embedded in a rarefied area or adjoining an unerupted tooth (Fig 518) Under the microscope calcareous bodies representing enamel, dentine and cementum are seen lying in a matrix of cellular connective tissue (Fig. 519) Some of these calcareous bodies represent small, imperfectly formed teeth. In the tumor inconspicuous strands of compressed epithelium of the basal-cell type (enamel epithelium) may be found (Fig 519, C) Unlike the soft or undifferentiated odonto-





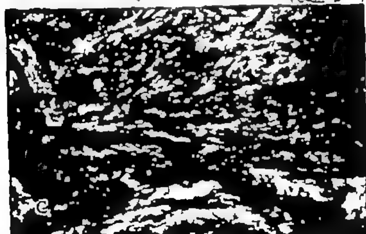


FIG. 519 Photomicrographs from a case of hard odontoma (A) and (B) show calcified bodies present in the tumor In (B) several small imperfectly formed teeth are seen. (C) shows the strands of compressed enamel epithelium found in odontomas. (Illustrations for Fig 418 and Fig. 419 by courtesy of Dr T Blum, The New York Institute of Clinical Oral Pathology)

mas, which are infiltrating tumors with a tendency to recur these hard odontomas are distinctly benign and do not recur after surgical excision.

Epulides. The term epulis ("on the gums") has a purely regional significance but is unfortunately commonly used as a diagnostic term to designate gingival neoplasms.

In a series of 150 cases classified clinically as epulis, and microscopically studied in this laboratory 12 were definitely inflammatory and are not included in this study In 6 other instances, also excluded, the tumors were basal-cell adenomas of the salivary type or early adenocystic basal-cell or squamous-cell cancers arising from the oral epithelium A group of 15 fibromas related to the nerve sheath or to the submucous tissue were also ruled out Angiomas were particularly common and in 35 cases an increase in the size and number of capillaries was a prominent feature The remaining lesions were microscopically classified as osteomas or alveolar giant-cell tumors The diagnosis and treatment of these lesions is discussed in Chapter 15

While angiomatous lesions, granulomas and hypertrophied epithelium commonly classed as epulides are not peculiar to the alveolar ridge, they are frequently found in this region during pregnancy Lesions of this group are variously referred to as epulis gravidarum, pregnancy tumors or pregnancy gingivitis.

Pregnancy Tumors of the Alveolar Margins. Epithelial hypertrophy granulation tissue and angiomatous areas are frequently found in the gums of pregnant women. More rarely alveolar giant-cell tumors or fibromas may grow rapidly during this period. The changes are most common in the first half of gestation and in younger women They make their appearance more frequently in the first than in subsequent pregnancies, and are more common in the upper than the lower jaw



Fig 520 (No 46842) Pregnancy tumor of the angiomatous type first observed at the end of gestation in a woman of 30

Ziskin, Blackberg and Stout, in a study of 416 pregnant women, found 158 with some form of pregnancy gingivitis. In most cases the gums show localized red swellings which bled easily the swelling overlapping the margins of the teeth in the anterior or bicuspid area. Many of these women show unhygienic mouths and give a history of gingival irritation preceeding pregnancy Early in gestation there is a thickening of the epidermal covering over the affected areas. This does not necessarily progress during gestation According to the authors just cited, the most significant microscopic change is hypertrophy of the epithelium with down-growth of the epithelial pegs. These authors injected monkeys and rats

with pregnancy urine with suggestive results, but did not determine whether the experimental gingival changes were caused by the estrin or the anterior pituitary-like hormone present in the urine.

Blum studied a series of 16 cases of pregnancy tumor. With the exception of four cases (three of giant-cell tumor and one of hypertrophy of the epithelial tissue) all were characterized by an increase in vascular elements and wandering cell infiltration. Blum concluded that pregnancy tumors are apparently blood vessel tumors originating from the deeper structures of the gingiva, the inflammatory changes being secondary. A disturbance of the endocrine balance was considered an etiologic element. The authors believe that increased parathyroid hormone in pregnancy is a factor. Local excision with strict oral hygiene is recommended. If not treated, these lesions show a tendency to recur with subsequent pregnancies.

In the present study, according to the history given, only one hemangioma and three giant-cell epulides had their onset during gestation (Fig. 520). While angiomatous proliferation and a epithelial hypertrophy are the predominant microscopic changes in pregnancy gingivitis, both vascular and epidermal changes are not uncommon during pregnancy in other regions of the body. Angiomas of the skin may show increased activity at this period. Increase in the parathormone content of the blood during the first third of pregnancy has been recorded by Hamilton and it is not unlikely that this may account for the increased vascularization about the teeth and occasional giant-cell lesions occurring during this period. Thickening of the epithelial covering of the cervix occurs with increase in estrin during pregnancy and such epithelial changes can be produced experimentally with this hormone on this and other epidermal surfaces (Overholser and Allen).

TABLE 86. COMPARISON OF ALVEOLAR AND CENTRAL GIANT-CELL TUMORS OF THE JAW

	Alveolar Giant-cell Tumor (Giant-cell Epulis)	Central Giant-cell Tumor
Number of cases	51	25
Maximum age distribution	10-20 years	10-20 years
Predominant site	Alveolar border, canine and bicuspid teeth	Symphysis, angle of mandible, medial wall of *antrum*
Average duration of symptoms	2½ years	6 months
Average size of tumor	Approximates 1 cm.	Approximates [illegible] cm.
Symptoms	Visible swelling, overlapping teeth, no pain	Central expansion of jaw, swelling of face, pain
Microscopic structure	Many multinucleated giant cells	Many multinucleated giant cells
Treatment	Excision with cauterization or irradiation	Curettage with cauterization or irradiation

Alveolar and Central Giant Cell Tumors of the Jaws. Benign tumors containing numerous giant cells occur along the alveolar margins (epulis) and centrally within the osseous substance of the upper and lower jaws. The giant-cell epulis is discussed in Chapter 15 and central giant-cell tumors of the jaw in Chapter 13. Both alveolar and central giant-cell tumors of the jaws occur at earlier ages (10 to 25 years) than giant cell tumors of the long bones (after 20 years). A comparison of the clinical features of these two groups of tumors is given in Table 86.

Giant-cell epulis and central giant-cell tumor of the jaws may occur as initial manifestations in hyperparathyroidism. In such cases the tumor formation apparently follows the liberation of calcium during the process of bone resorption and the parathyroid glands are the seat of a benign adenoma. Apparently the cases of alveolar

giant-cell tumor which have their onset or increase in size during gestation are also affected by an increase in parathormone in the blood which occurs in early pregnancy Roentgen studies of the long bones and a determination of the calcium and phosphorus values in the blood should be made before undertaking treatment



Fig. 521 (No 38560) Roentgenogram of a giant-cell tumor occurring near the left angle of the mandible. Note the trabeculae traversing the cystic area.

The epulis, when not too large, may be treated by simple excision with cauterization, and without extraction of the neighboring teeth. Recurrence is rare with such treatment. External irradiation with roentgen rays or radium is also successful in most instances (Soiland) but care must be exercised to avoid irradiation osteitis.

The treatment of giant-cell tumor of the jaw should be conservative. Thorough curettage followed by chemical cauterization is preferable in the lower jaw In large tumors of the upper jaw particularly those extending to the temporal fossa or into the recesses of the antrum, irradiation should be combined with curettement. These tumors show a tendency to recur when invading the temporal fossa or the body of the sphenoid. With tumors in other localities in the upper jaw and particularly the lower



Fig. 522 Roentgenogram of a benign giant-cell tumor of the mandible in a girl of 9 years. *The patient was well 15 years later*

jaw the majority of the patients remain well following curettement.

Benign Ossifying Tumors of the Jaw Ossifying lesions of the jaw occur upon the alveolar ridge beneath the gum (ossifying epulis) on the hard palate (torus palatinus) in the mandible between the symphysis and the angle and in the maxilla in the region of the antrum. The more cellular growths occur in patients under the age of 20 years. Although many of these more cellular growths are regarded clinically as fibrosarcomas, the present study indicates that they are benign. When growing peripherally these neoplasms are difficult to distinguish from nonsuppurative ossifying periostitis, which is an exceedingly rare condition in the jaws. They may be associated with infection or trauma or may arise spontaneously They may be preceded by the extraction of a tooth or marked by painless swelling of the face. In rare instances, such a localized swelling on or near the gum may be incised under the impression that it is a "gum boil" In the larger lesions, bone resorption is visible in the roentgenogram. In rapidly growing tumors

of the antrum, obstruction of the nasal passage or epistaxis may occur Pathologically these lesions may be conveniently divided into two groups. The more cellular growths



Fig. 523 Gross specimen of a giant cell tumor in which is embedded a nonerupted tooth.

occur in younger individuals and may be termed ossifying fibromas. Tumors of the second group are composed histologically of adult compact bone, occur in older individuals and may be classed as osteomas.

Ossifying Fibromas. Of 30 ossifying fibromas in the present series, slightly over two-thirds occurred in patients under 30 years of age. They resemble similar growths in the cranial bones described in the preceding chapter A painless swelling of slowly increasing size is produced, with an average duration of five years. The tumors are of bony hardness and are firmly



Fig. 525 (No 40478) Roentgenogram of a large ossifying fibroma of the lower jaw

attached to the jaws. In the upper jaw the region of the antrum and in the lower jaw the body of the mandible are usually affected. Inflammatory symptoms were

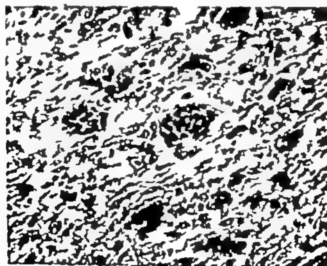


Fig. 524. (No. 51692) Photomicrograph of a central giant-cell tumor of the jaw



FIG 526 Roentgenogram of ossifying fibroma of the mandible

noted in one-fifth of the cases and trauma less frequently Usually swelling was the first symptom. Occasionally the swelling interfered with dentition or obstructed the nasal passages, but in most instances change in configuration of the face alone was noted.

Tumors in the region of the mandible give a fairly characteristic picture in the roentgenogram. The projecting tumor mass is of regular contour and less dense than normal bone (Fig 525) If of large size, the area of rarefaction is accompanied by subperiosteal ossification, which gives to the projecting margin a distinct outline. Where the tumor overlaps normal osseous structures, a shadow of increased density is produced. A comparison of the affected with the nonaffected side is important in differentiating these growths from bone destroying lesions such as benign giant-cell tumor and carcinomas of the mucous membranes invading the jaws. Malignancy can be ruled out by the smooth contour of the mass (Fig 527)

In the region of the antrum the affected side shows increased density or cloudiness. The lateral views depict a widening of the normal bone, merging into a domelike area of less density Both the dome of the tumor and its under surface toward the antrum often show a dense shell. In most instances, the tumors arise outside the antrum and encroach upon this cavity or extend down



FIG 527 (No. 39620) Roentgenogram of an ossifying fibroma in the region of the antrum. The region of expansion has a clearly outlined and definite margin.

ward toward the alveolar border pushing the teeth downward. In no case was peripheral irregularity found in the form of periosteal spicules forming at right angles to the jaw The granular resorption or increased density produced by osteomyelitis is not present in these lesions. The absence of multilocular rarefied areas or distinct trabeculae distinguishes these growths from benign giant-cell tumors and adamantinomas.

At operation there is a shell of osseous tissue beneath which lies a mass of fibrous material containing scattered osseous spicules (Fig. 529) Because cortical bone is produced at the margin of these growths, and because the pre-osteoid nature of the connective tissue beneath is generally not recognized, they have been traditionally

classed as central fibromas or as central fibrospindle-cell sarcoma (Fig 530) The modern tendency is to identify them histologically with fibrous dysplasia (Fig 532) (Schlumberger) In the present series, the majority of the growths were related to the more benign and definitely ossified osteomas of the jaw and arose from the subperiosteum. They were neither central, nor purely fibrous, nor sarcomatous in nature as is generally supposed. Microscopically irregular trabeculae of bone are scattered in a stroma of cellular connective tissue, the bone trabeculae being surrounded by many large round osteoblasts. Many psammoma like bodies of osteoid tissue (Fig 531) lie free in the connective tissue, unattached to bone trabeculae. These peculiar detached osteoid bodies are typical of ossifying tumors of the membranous bones and are also seen in the osteomas of the cranial bones. Such signs of ossification rule out fibrosarcoma. These tumors can be distinguished from osteogenic sarcoma by the absence of malignant nuclei and atypical mitotic figures in the spindle cells and osteoblasts.



FIG. 528 Roentgenograms of two views of an osteoma of the orbit.

While these tumors may recur after excision, metastases were not proved in any of the cases in this series. In the majority of cases followed more than five years after operation, the patients remained well Many of the cases, however were treated by needlessly radical resection. In adults with slowly growing tumors of this type, the lesion should be watched rather than operated upon during the period of growth. The preferable treatment is careful exci-



FIG. 529 (No. 24111) Gross specimen of an ossifying fibroma, showing the lobulated and encapsulated character of the growth. This lesion was formerly classed as a central fibrosarcoma of the jaw (previously published by Bloodgood)

sion with cauterization of the surrounding region, during a period of quiescence. Even with recurrences such treatment should be tried when more radical removal means mutilation. Up to the present time, the cases in this series treated by irradiation have not responded favorably



FIG. 530 (No. 52854) Low-power photomicrograph of an ossifying fibroma. One side of the alveolar margin encasing the tooth has been eroded by the tumor which has embedded itself within the osseous structure of the jaw Along its outer margin the tumor is laying down a shell of new bone. Although the tumor is arising subperiosteally it gives the appearance of a central origin.

Osteomas of the Jaw Osteomas of the jaw may be looked upon as a more differentiated form of ossifying fibroma. The patients with such growths are older the duration of symptoms is shorter and the size of the tumor is less than in the corresponding series of ossifying fibromas. For the osteomas, the average age is 40 years as compared with 14 years and the average duration of symptoms 14 months as compared with 45 months in the ossifying fibromas (Table 87)

The osteomas are usually symptomless, bony swellings occurring along the alveolar margin the zygoma, hard palate or man

TABLE 87 COMPARISON OF MAJOR FEATURES OF BENIGN OSSIFYING FIBROMAS AND OSTEOMAS

	Ossifying Fibromas	Osteomas
Number of cases	30	40
Average age	14 years	40 years
Predominant site	Body of mandible or region of antrum	Alveolar borders, zygoma, hard palate
Duration of symptoms	45 months	14 months
Size of tumor	Over 5 centimeters	Under 5 centimeters
Density of tumor	Less than normal bone	Greater than normal bone
Symptoms	Swelling, interference with dentition or breathing	Swelling
Microscopic structure	Large amounts of proliferating fibrous tissue, free osteoid spicules	Adult laminated bone, small amount of hyalinized tissue
Treatment	Excision with cauterization	No treatment or simple excision
Recurrence	15 per cent	None

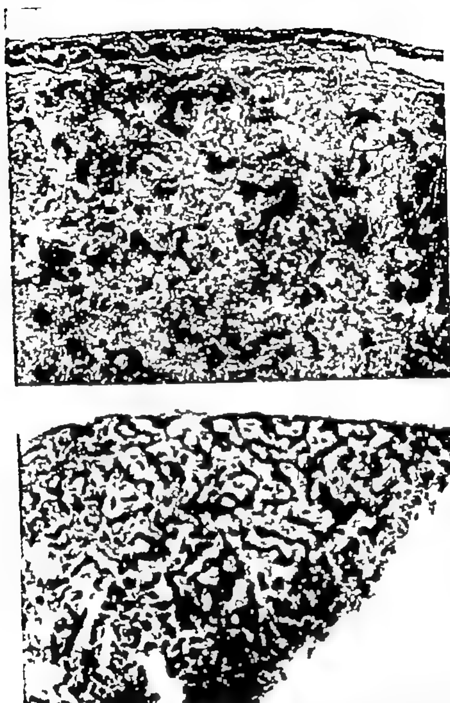


FIG. 531. (Nos. 46392 and 39620) Photomicrographs of ossifying fibromas and spongy osteoma of the jaws. (*Top*) shows the cellular character of the stroma and irregular ossified bodies. (*Bottom*) shows a transition to an osteoma. The histology is similar in some respects to that of osteoid-osteoma.



Fig 532 Photomicrographs of ossifying fibromas with histologic features similar to fibrous dysplasia of the long bones.

dible. They seldom involve the body of the maxilla or mandible and interference with mastication or respiration is rare. A history of infection or trauma is less common than in the more cellular ossifying fibromas. In the roentgenogram a small domelike swelling of increased density is seen (Fig 533) Occasionally these growths may be larger or lobular in outline but the margins remain dense and clearly defined. At operation the tumor lies like a button on the surface of the underlying cortical bone, being attached only at the center of its under surface (Fig 534) Microscopically a small amount of acellular fibrous tissue overlies the surface. Lamellae of dense bone with small haversian spaces predominate. Osteoblasts and connective tissue are inconspicuous (Fig 535) This histologic picture is typical of the so-called eburnated osteomas. At other times, the osteomas may be of the spongy type, with more widely



Fig. 533 (No 28905) Roentgenogram of osteoma in the region of the zygoma.

separated trabeculae of bone and slightly increased amounts of vascular fibrous tissue. This microscopic variety may merge with the cellular ossifying fibromas. In neither the eburnated nor the spongy osteoma is there a histologic resemblance to osteogenic sarcoma. In the spongy osteomas and in the ossifying fibromas, however the histologic picture is similar to osteoid osteoma and to fibrous dysplasia, respectively found in the long bone.

Both the osteomas and ossifying fibromas apparently arise from the subperiosteal layers of the jaws. Ossification in the overlying fibrous tissue results in compact bone formation, and below this is accompanied by vascularization and resorption of the underlying cancellous bone which gives to many of these growths their apparent central origin.

Treatment The prognosis of osteomas is good, unless they are located near a vital structure such as the orbit or upper nasal passages. In most instances surgical interference is not imperative. The more spongy growths may be chiseled from their base without the probability of recurrence. In the rare cases in which the histologic picture resembles ossifying fibromas, the treatment should be that described for the latter growths.

SARCOMA OF THE JAW

Sarcoma of the jaws is fortunately a rare condition. Öhngren in a series of 187 cases of malignancy in the region of the antrum, lists 15 cases of sarcoma, of which 2 were osteogenic and 3 possibly Ewing's sarcoma. The remainder arose in the overlying soft parts. In the present series of 36 cases, there were 17 osteogenic sarcomas (10 of the sclerosing type and 7 containing cartilage) and 19 were classified as Ewing's sarcoma.

Osteogenic Sarcoma Sclerosing or Ossifying Form. Ten cases of osteogenic sarcoma producing bone or osteoid material were recorded in the present series. These tumors with one exception, occurred in adults at ages varying from 17 to 65 years. The youngest patient was a negro girl aged 13, who remained well over 10 years following resection. The tumors grow rapidly and symptoms are of approximately 2 months duration. The upper and lower

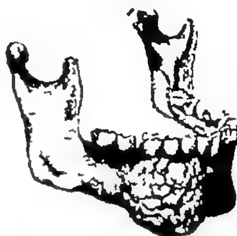


FIG. 534 Sketch of a museum specimen of osteoma of the mandible (after Perthes)

jaws are involved with equal frequency. In the region of the antrum, nasal obstruction and a foul or bloody discharge were recorded in three instances. In two of these cases, exophthalmos rapidly followed. In



FIG. 535 (No. 14016) Photomicrograph of an osteoma, showing the thin capsule of hyalinized connective tissue overlying dense trabeculae of adult bone.

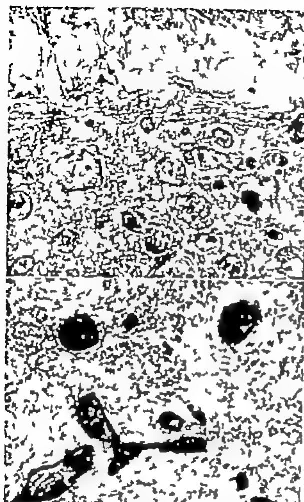


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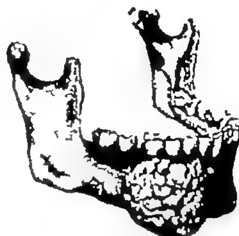


FIG. 534 Sketch of a museum specimen of osteoma of the mandible (after Perthes)

jaws are involved with equal frequency In the region of the antrum, nasal obstruction and a foul or bloody discharge were recorded in three instances. In two of these cases exophthalmos rapidly followed. In



FIG. 535 (No. 14016) Photomicrograph of an osteoma, showing the *thin* capsule of hyalinized connective tissue overlying dense trabeculae of adult bone.



FIG 532 Photomicrographs of ossifying fibromas with histologic features similar to fibrous dysplasia of the long bones.

dible They seldom involve the body of the maxilla or mandible, and interference with mastication or respiration is rare. A history of infection or trauma is less common than in the more cellular ossifying fibromas. In the roentgenogram a small domelike swelling of increased density is seen (Fig 533) Occasionally these growths may be larger or lobular in outline but the margins remain dense and clearly defined. At operation the tumor lies like a button on the surface of the underlying cortical bone, being attached only at the center of its surface (Fig 534) Microscopically a small amount of acellular fibrous tissue overlies the surface. Lamellae of dense bone with small haversian spaces predominate. Osteoblasts and connective tissue inconspicuous (Fig 535) This histol picture is typical of the so-called eburna osteomas. At other times, the osteomas r be of the spongy type, with more wic



FIG. 533 (No 28905) Roentgenogram of osteoma in the region of the zygoma

separated trabeculae of bone and slightly increased amounts of vascular fibrous tissue. This microscopic variety may merge with the cellular ossifying fibromas. In neither the eburnated nor the spongy osteoma is there a histologic resemblance to osteogenic sarcoma In the spongy osteomas and in the ossifying fibromas, however the histologic picture is similar to osteoid osteoma and to fibrous dysplasia, respectively found in the long bone.

Both the osteomas and ossifying fibromas apparently arise from the subperiosteal layers of the jaws. Ossification in the overlying fibrous tissue results in compact bone formation, and below this is accompanied by vascularization and resorption of the underlying cancellous bone which gives to many of these growths their apparent central origin

Treatment The prognosis of osteomas is good, unless they are located near a vital structure such as the orbit or upper nasal passages. In most instances surgical interference is not imperative. The more spongy growths may be chiseled from their base without the probability of recurrence. In the rare cases in which the histologic picture resembles ossifying fibromas, the treatment should be that described for the latter growths.

SARCOMA OF THE JAW

Sarcoma of the jaws is fortunately a rare condition. Öhngren, in a series of 187 cases of malignancy in the region of the antrum, lists 15 cases of sarcoma, of which 2 were osteogenic and 3 possibly Ewing's sarcoma. The remainder arose in the overlying soft parts. In the present series of 36 cases, there were 17 osteogenic sarcomas (10 of the sclerosing type and 7 containing cartilage) and 19 were classified as Ewing's sarcoma.

Osteogenic Sarcoma Sclerosing or Ossifying Form Ten cases of osteogenic sarcoma producing bone or osteoid material were recorded in the present series. These tumors, with one exception, occurred in adults at ages varying from 17 to 65 years. The youngest patient was a negro girl aged 13, who remained well over 10 years following resection. The tumors grow rapidly and symptoms are of approximately 2 months duration. The upper and lower



FIG. 534 Sketch of a museum specimen of osteoma of the mandible (after Perthes)

jaws are involved with equal frequency In the region of the antrum, nasal obstruction and a foul or bloody discharge were recorded in three instances. In two of these cases, exophthalmos rapidly followed. In



FIG. 535 (No. 14016) Photomicrograph of an osteoma showing the thin capsule of hyalinized connective tissue overlying dense trabeculae of adult bone.

the lower jaw a rapidly increasing swelling, with loosening of the teeth, bleeding, and secondary infection, occurred. Only two of these patients survived beyond a two-year period, although radical resection, with or without irradiation, was employed with few exceptions.

In the roentgenogram irregular dense foci of new bone production are to be seen, alternating with areas of bone destruction If proper views are taken, the margin of the tumors will show a periosteal reaction with occasional spicule formation extending at right angles (Figs. 536, 537) Under the microscope these tumors do not differ from sclerosing osteogenic sarcoma arising subperiosteally in the long bones. Irregular osseous or osteoid spicules surrounded by large numbers of malignant osteoblasts are embedded in extremely cellular connective tissue (Fig. 539) In rare instances, the large amounts of connective tissue make the lesions difficult to distinguish from benign ossifying fibroma.

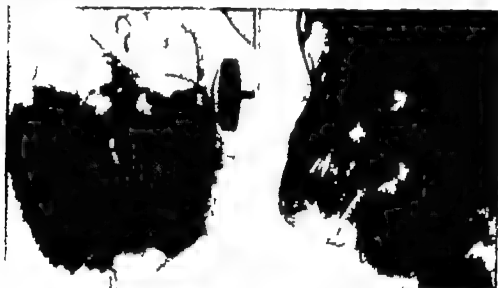


Fig. 536 Roentgenograms of osteosarcoma of the jaw (*Left*) Sclerosing osteogenic sarcoma of the upper jaw (Memorial Hospital, New York) (*Right*) Osteogenic sarcoma of the lower jaw producing a mottled area of bone destruction, followed by pathologic fracture.

Osteogenic Sarcoma Containing Cartilage—Chondrosarcoma Chondrosarcomas of the jaw apparently arise from benign cartilaginous rests embedded in the mandible near the symphysis or at the angle. In most instances the growth of the tumor is not rapid and a year or more is allowed to elapse before treatment. None of the seven cases recorded in the present series was situated in the maxilla and all of them were in adults. Cartilaginous tumors arising in the substance of the maxilla have not been recorded, to our knowledge, and should not occur in this membranous bone. Öhngren, however has reported one case of osteogenic sarcoma with cartilage invading the antrum from the region of the ethmoid. The tumor obstructed the nose and filled the maxillary sinus. The patient had had a previous operation for nasal polyp followed by prompt recurrence, but was well at the time of the report, nearly five years after treatment.

In the roentgenogram, these lesions produce an area of osteoporosis which extends rapidly to either the alveolar or lower margin of the mandible (Fig 540 A and B) The extension of the tumor is accompanied by pain, and the shell of bone about the area of destruction rarely remains intact. Occasionally in one or more areas a cystlike expansion may be produced, but erosion

without expansion is the rule, distinguishing these growths from benign tumors.

Under the microscope these lesions show islands of adult cartilage with areas of myxomatous tissue or fetal cartilage. Islands of calcification or new bone may be present, and in one instance in this series the first impression of osteochondroma was later revised to chondrosarcoma. It is safest to look upon all cartilaginous lesions of the jaw as potentially malignant and to treat them radically

All the tumors in the present series ultimately proved fatal regardless of the form of treatment. Repeated local recurrence however is the rule before distant metastasis occurs. Three of the patients in this series had repeated operations for recurrence One patient operated upon four times and given several radium treatments over a period of seven years, remained symptomless for seven years thereafter At the end of that time the patient was treated for a final local recurrence and two



Fig. 537 (No 2138) Roentgenogram of the gross specimen from a cured case of osteogenic sarcoma of the lower jaw Previously published by Bloodgood.



Fig. 538. Roentgenograms contrasting osteogenic sarcoma (*left*) and chronic osteitis (*right*) of the mandible.



FIG. 539 (No. 28394) Photomicrograph of a sclerosing osteogenic sarcoma of the lower jaw



FIG. 540 (Nos. 48684 and 23665) Roentgenogram and photomicrograph of chondrosarcoma of the lower jaw In the case shown in the roentgenogram a tooth had been extracted at the tumor site because of pain. Failure to relieve the pain and increasing bone destruction were interpreted elsewhere as osteomyelitis.

years later died of cerebral metastases, sixteen years after the first operation. In another case in which resection and radium treatment were combined death occurred from cerebral metastases three years after the first treatment.

Ewing's Sarcoma of the Jaw So-called round-cell sarcoma of the jaw was recorded in 19 cases in the present series. The extremely small size of the cell the uniformly dense nucleus, and the scanty cytoplasm were histologically characteris-

tic of Ewing's sarcoma found in the long bones (Fig 541) In three instances the possibility of a highly cellular and rapidly growing carcinoma or fibrosarcoma composed of oat cells could not be ruled out. Seven of these lesions occurred in children and six in young adults under the age of 30 The upper and lower jaws were affected eight years after the excision of the tumor and postoperative irradiation by means of radium with low filtration placed within the bone cavity Radical excision with cauterization or resection and excision combined with irradiation were the methods of treatment employed in this series without notable benefit

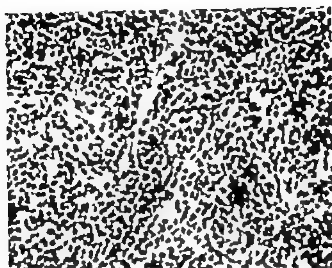


FIG. 541 (No 25634) Photomicrograph of Ewing's sarcoma of the jaw

with equal frequency With three exceptions, the duration of the symptoms (pain and swelling) was exceedingly brief the average being under one month, a very unusual finding in lesions of the jaw

Formerly Ewing's sarcoma was considered extremely rare in the jaw (Bloodgood) but the tumors in the present group are fairly typical clinically and pathologically The roentgenogram, however is not characteristic. Irregular areas of bone destruction are the most common feature but expansion of the cortex or periosteal new bone may be visible.

In those cases in the present series treated by adequate irradiation the tumor proved radiosensitive diminishing rapidly *in size*. In no case, however was a cure established. Recently Thoma has recorded two cases of Ewing's sarcoma in children with microscopic verification. In one of these cases, registered with The American College of Surgeons, the patient is well

So-called Fibrosarcoma of the Jaw Although central fibrosarcoma is repeatedly reported in the older literature, no verified cases of this type are recorded in the present series. In one instance sarcoma of the nerve sheath invaded the bone by direct extension in a fashion similar to that found in the long bones (Geschickter)

Generalized Skeletal Diseases with Clinical Onset in the Jaws. Both Paget's osteitis deformans and von Recklinghausen's fibrocystic disease may have their clinical onset in the region of the jaws. Enlargement of the jaw produced by large deposits of porous bone and characterized roentgenographically by widening and increase in the size of the trabeculae may antedate by many years the appearance of Paget's disease in the rest of the skeleton. This combination of so-called *leontiasis* ossium of the face with Paget's *disease* of the skeleton occurred in 3 of 30 cases of Paget's disease



FIG. 542. (No 43924) Photographs of a patient with Paget's disease of the upper jaw

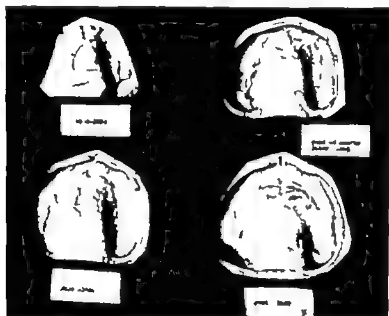


FIG. 543. Plaster impressions made over a period of six years, indicating the increasing size of the maxilla in the patient shown in Figure 542. (From Dr Grant Ward, Baltimore, Md.)

recorded in this laboratory One of these cases is illustrated here (Fig 542)

In two instances of multiple osteitis fibrosa cystica occurring in young adults with disturbances in the blood calcium and demonstrable parathyroid tumors at operation, the onset of the condition was with giant-cell tumor of the alveolar margin. Similar cases have been reported in the literature and in the presence of rapidly growing tumors of the giant-cell variety on the alveolar margins, the skeleton should be studied carefully for other lesions. In rare instances, a central giant-cell tumor of the lower jaw may undergo spontaneous fibrosis and liquefaction, being converted

into a cyst of the osteitis fibrosa type, such as occurs in the long bones.

Thoma has described a case of multiple myeloma with initial involvement in the lower jaw

MALIGNANT EPITHELIAL TUMORS

Carcinoma of the antrum is sometimes considered as a primary disease of the upper jaw It is the most common malignant condition of the maxillary region. The majority of these tumors occur in adults after the age of 50 years and terminate fatally within 2 years of diagnosis The prevailing histologic form is epidermal carcinoma of the keratinizing or nonkeratinizing type, occasionally with a papillary structure indicating an origin in benign papilloma. Basal-cell tumors either adenocystic or mixed salivary in type, are less common, and rarely adenocarcinoma showing a relationship to the mucous glands is recorded.

These tumors produce swelling or bulging of the maxilla and distort or erode the walls of the antrum. A fungating tumor on the hard palate, loose teeth, trigeminal neuralgia and exophthalmos are the common symptoms. These antral tumors are closely allied in their clinical and pathological behavior to intranasal or ethmoidal tumors. From the standpoint of differential diagnosis, however they must be included among lesions of the upper jaw since there is equal possibility of antral tumors invading the jaw bones or osseous and dental tumors of the jaw invading the antrum.

Invasion of the upper jaw by carcinoma of the antrum usually occurs intra-orally in the region of the hard palate or in the socket of a tooth previously extracted for pain or looseness. Such carcinomas arise in the anterior inferior portion of the antrum and in the roentgenogram show expansion or distortion of the antral walls, clouding of the antral cavity and destruction or decalcification of the lower portion of the maxilla.

The tumors may be approached surgically through the hard palate or anteriorly by an incision through the upper lip and about the nose, with reflection of the cheek. They are best extirpated by electrocoagulation followed by radium or radon applications inserted into the antral cavity Previous to the use of irradiation there was only one five-year cure recorded in a series of 56 cases in this laboratory Ohngren reports 16 per cent of five-year cures in a series of 116 cases of epidermal and basal cell cancers treated by combined electrocoagulation and irradiation. The tumors tend to metastasize to the pharyngeal lymph nodes and to the deep jugular chain of nodes at the bifurcation of the carotid. Cerebral abscess meningitis and hemorrhage are among the principal causes of fatality The prognosis is somewhat better in papillary epidermal carcinoma and in the basal-cell cancers of the mixed salivary type. Unfortunately these represent but a small percentage of the entire group



FIG. 544. (No. 29800) Roentgenogram of a case of squamous-cell carcinoma of the gum invading the lower jaw

Invasion of the lower jaw by carcinoma occurred in eight cases in the present series. In six cases epidermoid carcinoma infiltrated through the lymphatics of the mental

foramen from the lip or extended around a tooth from the mucous membranes of the floor of the mouth. All of these cases had originally been treated at their primary sites as benign conditions, and the true nature of the disease was discovered only after osseous destruction had occurred. In one instance the lesion was adenocystic basal-cell carcinoma in the remaining cases, squamous-cell cancer In the roentgenogram bone destruction without evidence of new bone formation was the outstanding feature (Figs. 544 and 545) Usually the area of destruction, because of its irregular and worm-eaten appearance and because of the absence of new bone formation, can be diagnosed as carcinomatous in the roentgenogram. The bone erosion extends to the surface of the jaw In one case, however a multilocular character simulated adamantinoma, and in another instance the area of erosion surrounded a nonerupted tooth, simulating a dentigerous cyst. Carcinoma of the lower jaw like cancer of the antrum in the upper jaw should be treated by cauterization and irradiation. The prognosis is equally grave.

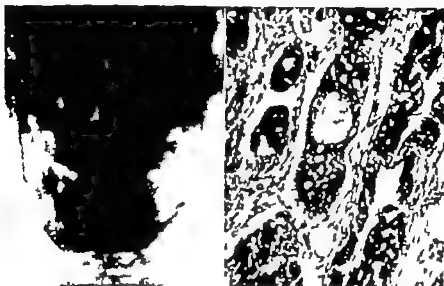


Fig. 545 (No 54814) Roentgenogram and photomicrograph of adenocystic basal-cell cancer invading the mandible. (Case of Dr Vernon Norwood, Baltimore, Md.)

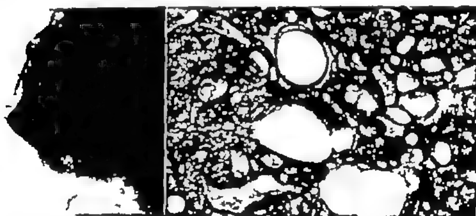


Fig 546. (No. 27532) Roentgenogram and photomicrograph of a carcinoma of the thyroid with metastasis to the mandible.

Although carcinoma metastasizing to

bone is relatively common condition the upper and lower jaw are rarely involved. Only three cases are recorded in this laboratory In one of these the primary tumor was an adenocystic basal-cell carcinoma originating in the mucous membrane of the nose, and in another instance carcinoma of the prostate invaded the lower jaw In both instances the entire skeleton was affected by carcinomatous deposits. In one additional case carcinoma of the thyroid gland of a low degree of malignancy produced an area of destruction in the mandible (Fig 546) Palliative irradiation is the only treatment that can be given in these cases.

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24

Tumors of Tendon Sheaths, Joints and Bursae

The articular structures, including joint cartilage, synovial membrane and joint capsule, and the *periarticular structures*—bursae, ligaments and adjoining tendons—have a twofold origin. The outer tissues are formed from connective tissue identical with that found in the superficial and deep fascia. On the other hand, intra-articular tissues and the ligaments, tendons and bursae nearest the joint are derived from precartilaginous tissue capable of forming both cartilage and bone. *This precartilaginous tissue is a portion of the persisting skeletogenic mesenchyme.*

Malignant tumors are equally rare in the fibrous structures and in those of precartilaginous origin. Benign tumors, which are not uncommon, affect most frequently the articular and periarticular structures which are developed from precartilaginous tissues. These neoplasms, including giant-cell tumor chondroma and osteochondroma, resemble in their character and behavior similar tumors in the bone.

Skeletogenic mesenchyme, destined to form both cartilage and bone, condenses at the site of the future skeleton in the early embryo Strands of this primitive tissue, *cutting across the future bone at right* angles, persist at the site of the future joints (Fig 547) By mucoid regression some of this tissue forms the joint cavity the surrounding condensation forming the synovial membrane. Other strands persist at the reflection of the joint capsule and at points of attachment of tendons and ligaments. Some of this tissue may regress at *these points to form* bursae.

Osseous, cartilaginous, or chondro-osseous tumors may be found at any of these sites. The most common are osteochondromas or exostoses, formed at the insertion of tendon in bone and commonly considered as bone tumors. This large group of benign tumors, situated at the junction of tendon and bone, has been discussed in Chapter 2. *Ossification of similar derivation* may occur at the muscular ends of tendons in cases of myositis ossificans progressiva. (See Chap. 16.)

Osteochondromas may develop in bursae, the so-called *exostosis bursata*, or they



FIG. 547 Photomicrograph showing the knee joint of a human embryo 14 cm. in length. The dense strands of mesenchyme cutting across the future bone at right angles are giving rise by mucoid regression to the joint cavity at (A) At (B) strands of this dense tissue are persisting to take part in the formation of synovial membrane, capsule and tendons.

may also form within the joint, embedded in the synovial membrane, extending along the ligaments and tendon as in osteochondromatosis of the knee joint. Some distance from the joint within the tendon, they occur sometimes in the form of aberrant *sesamoid bones*. *Osteochondromas*, therefore, are found in tendon, bone, bursae, joints and ligaments, and indicate the common *precartilaginous origin of these structures* in the embryo.

During the formation of the cancellous bone in the embryo, the resorption of calcified cartilage is accompanied by a proliferation of giant cells. This process may be the starting point for a benign giant-cell tumor of bone, and a similar process occurring at the site of osteochondromatous structures in tendons, joints, ligaments or bursae may give rise to giant-cell tumors embedded in these structures. The most common of these is the giant-cell tumor of the tendon sheath, found at the site of the *sesamoid bones*. This osteoclastic tissue also has the power of phagocytosing lipoid material and may *show xanthomatous cells*.



FIG. 548. Osteochondroma in the *tendo achillis of a white male aged 21*. The patient has remained well without treatment or change in the condition during the past twenty years.

Mucoid regression in precartilaginous tissue which forms the joint cavities may *occur in the adult joint cartilage to form* cysts or in the tendon sheath to form ganglia. The latter lesions are relatively common.

The fibrous structures of tendons, ligaments, and joints not related histogenetically to the skeletal tissues are also the seat of tumor formation. This fibrous tissue when giving rise to tumor formation resembles the primitive mesoderm and the epithelial like cells lining the synovial membrane. The majority of these growths are



FIG 549 Osteoma of the tendon sheath occurring in the flexor tendon of the finger

benign synoviomas and synovial sarcomas of the tendon sheath. Fibromas and fibrosarcomas may also occur Lipomas, also have been recorded. The vessels supplying the synovial membrane, including the blood and lymph vessels, may give rise to angiomas. A small number of these tumors *occurring in joints or tendons* have been described.

TUMORS OF THE TENDONS AND THE TENDON SHEATHS

Tumors of the tendon and tendon sheath are more frequent than those of joints and bursae. Rare benign tumors are osteochondromas and giant-cell tumors, all of which are *related to precartilaginous connective* tissue. The more common are the benign ganglia and synovioma. Synovial sarcoma is the most common malignant condition.

Osseous and Cartilaginous Tumors of the Tendon Sheaths

Both benign osteochondroma and chondrosarcoma *may arise within the tendon* sheaths independently of bone, just above the point of osseous insertion, where precartilaginous tissue normally persists. Seven benign osteochondromas in this loca

TABLE 88. ARTICULAR AND PERIARTICULAR TUMORS DERIVED FROM PRECARTILAGINOUS TISSUE

Osteochondromatous Changes	Mucoid Regressive Changes	Osteoclastic Regression
	Tendons	
1 Osteochondromas and chondrosarcomas of tendon sheath (9?) 2 Osteochondromas, chondromas and chondrosarcomas in relation to bone (400) 3 Myositis ossificans in relation to tendons (5)	1 Ganglia (120)	1 Giant-cell tumors (30) 2. Xanthomatous tumors (10)
	Joints	
1 Chondromatosis (13)	1 Cysts of joint cartilage and synovia (2)	1 Giant-cell tumors (3) 2. Synovial xanthomas with giant cells (5)
	Bursae	
1 Exostosis bursata (2) 2. Chondromas (2)	1 Adventitious bursae (4)	1 Giant-cell tissue with calcinosis (1) 2. *Symptomatic xanthoma* with diabetes (1)

Numbers indicate cases recorded in the authors series.

TABLE 89 TUMORS DERIVED FROM FIBROUS TISSUE AND VESSELS

	Fibrous Tissue	Vessels
Tendons and Joints	1 Fibromas (30) 2. Lipoma (4) 3. Benign Synovioma (60) 4 Synovial Sarcoma (35)	1. Hemangioma (2) 2. Lymphangioma (1)

tion occurred in our series, and reports of 15 additional cases were found in the literature (Fig 550) Patel reported a bilateral case in the Achilles tendon which interfered with walking, and included two additional cases in his discussion Janik reported two more cases of osteochondroma and cited six others. The latter were on the hand or foot, in adults, and the majority



A B

Fig. 550 (Nos. 31678 and 53888) Osteomas of the tendons about the ankle (A) Roentgenogram of an ossified lesion in the flexor tendon in a white male of 15 (B) Roentgenogram of a similar lesion in the tendo achillis in a white male aged 20 Both patients have been reported well for a period of over 5 years.

were diagnosed histologically as calcified chondromas. Buxton's case, on the ring finger in the flexor tendon, had the size and appearance of a sesamoid bone and was ossified. Buxton also described a case of multiple cartilaginous tumors attached to the tendons of the hand in the museum of King's College Hospital

All of our cases were in adults who have remained well over *five years, two without* operation Two were near the elbow three in the Achilles tendon, *one in the* quadriceps above the patella, and another anterior to the ankle joint *Another was on the* flexor surface of a finger These lesions occurred without accompanying arthritis or tenosynovitis.

In addition to the benign cases two chondrosarcomas of the tendon are recorded. The history of one of these cases is given in the legend accompanying Fig 551 A somewhat similar case associated with chondromatosis of the knee joint has been reported by Jones and another by Kienböck. Buxton has cited a case of chondrosarcoma on either side of the Achilles tendon in a girl aged seventeen, the specimen being preserved in the Royal College of Surgeons Museum.

The microscopic character of *benign* osteochondromatous lesions is similar to that of osteochondroma of the skeleton the *malignant* cases are similar to chondrosarcoma of bone. The masses of cartilage vary from adult to fetal forms and are separated into lobules by unusually abundant amounts of fibrous tissue. In the benign



FIG 531 (No 43288) Chondrosarcoma in the tendo achillis in a white female aged 31 years. Pain and tumor formation had been present for two years, at the site of an old injury to the heel. Examination showed a rubbery mass just above the os calcis posteriorly. The roentgenogram depicts a translucent mass about the tendon, with a periosteal reaction along the fibula. Exploration was performed and amputation done below the knee, upon a microscopic diagnosis of chondrosarcoma. The patient was reported well 5 years later

cases calcification and ossification appear beneath the capsule of the lobules. In the malignant cases cellular precartilaginous connective tissue is found in this location.

The cycle of histologic changes in these tumors—from connective tissue to cartilage, to bone—repeats the histogenesis of intracartilaginous ossification observed in the long bones. This suggests a derivation from undifferentiated precartilaginous foci.

The chondromata and osteochondromatous lesions in the tendons of non-neoplastic nature are more often seen in association with osteophytes in chronic osteo-arthritis and bursitis. The lesions give mild pain after repeated motion of the affected tendon. Severe symptoms are rare unless *trauma or infection occurs. When increased* rapidity of growth occurs, tumors, with the possibility of malignant change, must be considered. Excision should be performed with a good margin of healthy structures.

GANGLIA OF THE TENDON SHEATHS

The ganglion is a rather common cystic tumor occurring in adults about the wrist or ankle or on the flexor surface of the hand or the dorsum of the foot. Baumecker has reported one case and cited another in the region of the hip. The ganglion is composed of cystic spaces lined by connective tissue and distended with a gray jellylike substance. Usually the tumor is attached to the adjoining tendon sheath or joint capsule by a fibrous band but does not communicate directly with these cavities (Fig. 552). Since the time of Eilers (1746) the etiology and nature of these lesions have been in dispute. While they were formerly thought to be herniations from the joint cavity or tendon sheath, distended with synovial fluid, the more recent tendency is to regard them as cystic neoplasms of connective-tissue origin (since the work of Clarke in 1908). These cysts do not have a true endothelial lining, and in their histogenesis they show the same regressive changes in precartilaginous connective tissue that are found in the embryo during the formation of the joint cavities or are observed in later life in the formation of anatomic and adventitious bursae. Many of the so-called ganglia described as occurring in unusual locations are adventitious bursae.

The present series includes 150 of these small benign tumors which were excised and microscopically studied. One hundred were related to the tendon sheaths about the wrist. Of the exceptional cases, 4 were in the region of the ankle and one at the knee. All except two—in children of 2 and 11 years—were in adults. The number pathologically studied, however, by no means represents the frequency of these lesions, since many disappear after rupture through *injury or as a result of digital compression,*

which is a common mode of therapy Pain is rare. Treatment is usually instituted because the patient's attention has been attracted to the presence of the swelling. The tumors may recur after rupture. They may be cured by the injection of hypertonic solutions or by excision. Recurrence after excision is not uncommon and should be treated with sclerosing solution.

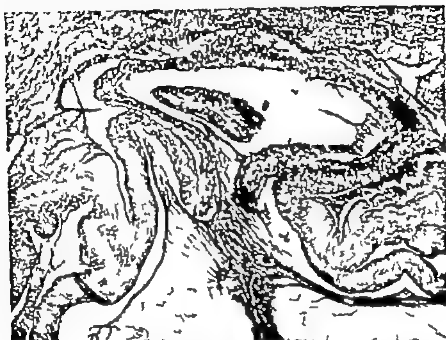


Fig. 532. (No 53737) Photomicrograph of a ganglion of the tendon sheath. The tumor was excised from a white woman of 35 years who had a swelling the size of a marble on the left wrist, on the radial side. Cystic spaces are being formed by mucoid regression in precartilaginous connective tissue. The lining of the cysts contains modified connective-tissue cells with an epithelial-like arrangement.

GIANT-CELL XANTHOMA OR BENIGN SYNOVIOMA OF THE TENDON SHEATHS

A fairly common, encapsulated fibroid tumor of small size occurs frequently in the tendon sheaths about the fingers, ankles and toes. Microscopically it is composed of connective tissue with a characteristic collagenous matrix enmeshing giant cells, blood pigment and occasional foam cells. The tumor may contain small, cystlike spaces, reminiscent of synovial tissue. The modern tendency is to call these growths benign synoviomas. In Chapter 15 a group of these tumors, in which giant cells were prominent, was described The tendency for osseous or osteoid material to appear in these growths and their relationship to aberrant sesamoid bone were emphasized

The characteristic location of these growths on the sheaths of flexor tendons, their encapsulation and their characteristic histologic features make diagnosis relatively easy In the gross, they have a yellowish-orange color and their removal by simple excision is easy Adults are usually affected. The duration of symptoms is in terms of years rather than months. The incidence of these tumors in the surgical pathology of military hospitals is higher than in civilian institutions, indicating that repeated trauma with vigorous manual labor or exercise is important in the symptomatology We have examined more than 100 of these tumors and have found malignant change in only one. This was in the

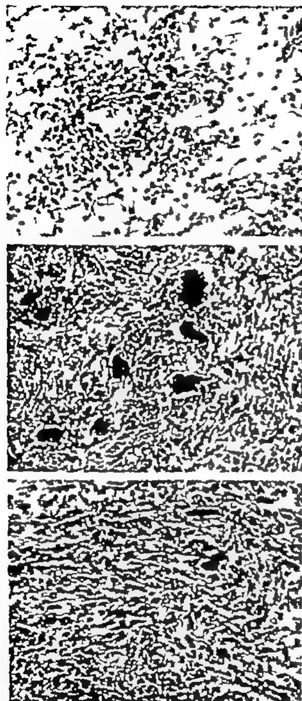


Fig 553 Photomicrographs of giant cell xanthoma of tendon sheath (*Top*) Xanthoma type (*Center*) Giant-cell type (*Bottom*) Synovial type

hand of a girl, aged 26, a mattress seam stress, who reported repeated trauma to the tumor in her work. The section of the tumor originally excised showed a charac teristic benign structure. The recurrent growth at the site of excision was a fibro-spindle-cell sarcoma.

In review of sections, we have been impressed with three separate histologic varieties. The most common is that in which the fibroid structure predominates, and the tumor can be termed a synovioma. A smaller group has a similar stroma, but fibrocartilage and collagen are prominent among the intercellular material and giant cells are an outstanding feature. This is the giant-cell tumor of the tendon sheaths which we have related to the sesamoid bones The least common is the xanthomat ous variant, in which the foam cells are the conspicuous feature (Fig. 553) When xan thoma cell predominate in tumors of the tendon sheath, the tumors are often multi ple and may be associated with hereditary hypercholesteremia. The nodules often appear on the elbows, knees and buttocks, and over the tendons of the hand and feet. These cases may be associated with fatal coronary disease (Bloom, Kaufman and Stevens)

The giant-cell tumors or synoviomas of the tendon sheaths, as previously stated, are usually small and benign. Beside the case of malignant change mentioned, two in our series recurred after removal, and three invaded bone. Bessessen has reported a recurrent case on the middle finger of the right hand in a man aged 27 Ragins found six cases in the literature with invasion of the bones. Simple excision usually cures.

Giant-Cell Tumor of the Patella

Giant-cell tumors of the patella are lesions homologous to those derived from smaller sesamoid bones about the hand and foot. Three cases are recorded in the laboratory In histology they were similar to giant-cell tumors of the tendon sheath, described above, and paralleled the same type of tumor occurring more frequently in the ends of the long bones. Bennett has recently reported a case and reviewed the literature. While these tumors of the patella are not common, benign chondroma

and cysts of this bone have also been reported, showing that pathologic changes similar to those described above for the smaller sesamoids also occur here. Neurnbergk has collected 37 tumors of the patella, reporting 2 giant-cell tumors and citing 8 others.



FIG. 554 (No 53116) Photomicrograph of a xanthomatous giant-cell tumor arising in a sesamoid bone in the sheath of the flexor tendon of the index finger The lesion was excised from a woman aged 48 who had noticed the swelling for one year At operation the mass was found within the tendon sheath. The section shows spicules of newly formed bone surrounded by a cellular stroma containing many giant cells. The remains of fibrocartilage were visible in the section indicating origin in a sesamoid bone

LIPOMA, FIBROMA AND SYNOVIAL SARCOMA OF THE TENDON SHEATHS

Connective-tissue tumors not related to precartilaginous and pre-osseous tissue are rare in the tendon and tendon sheaths. Strauss found 18 cases of lipoma in the literature definitely connected with the tendon sheath Two are recorded in our laboratory The majority of the cases reported were of the arborescent type some were simple lipomas all were attached to the sheath. The patients were young adults with symptoms of from one to nineteen years duration. The extensor tendons of the hand or foot are most frequently involved. The lobules of these lipoid growths, which are histologically typical lipoma are found immediately surrounding the tendons, which tunnel through the folds of fat. The sheath must be excised along with the tumor

Benign fibromatous tumors of the tendon are also uncommon. Buxton collected 13 fibromas from the literature. Torchiana recently cited a case in a woman aged 39 who had such a tumor in the palm of the hand, with recurrence after excision

One of our cases of typical fibroma was above and behind the clavicle in a girl of 15 in the tendon of the anterior scalenus muscle (Figs. 555 and 556) These tumors were definitely encapsulated and easily ex

cised. Their structure resembles very much exuberant scar tissue, disclosing bundles of collagen and long connective-tissue fibers. The cells, which are tightly packed, are surrounded by collagen fibers, which make the tumor far more dense and firm than nerve-sheath tumors, with which they may be microscopically confused.

In our material there are 30 cases of histologically typical fibromas, the origin of

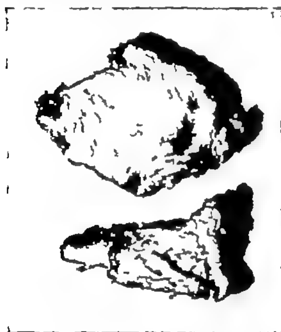


FIG. 555 (No. 48450) Fibroma occurring in the tendon of the anterior scalenus muscle. The patient was a girl aged 15 years, who had noticed the tumor above the clavicle for a period of six months.

which could be assigned to the tendons and tendon sheaths with reasonable assurance The majority of the patients were between 10 and 25 years of age, while the second largest group occurred between 35 and 45 years. There was one patient under ten and one over 50 years of age. Ten of the lesions were on the flexor or plantar surfaces of the hand or foot 8 were situated in the region of the elbow or forearm, 2 on the shoulder 3 over the cervical spinous processes, 3 in the region of the knee, and 2 on the leg The duration of the tumors varied between one and five years, and they rarely attain a size larger than that of a hen's egg

SYNOVIAL SARCOMA

Malignant tumors of connective-tissue origin involving the tendon sheaths, a synovial membrane of joints, are now referred to as synovial sarcoma. They are related in their histologic structure to the synovial membrane, and more frequently involve the tendon sheath and periarticular structures than the joint proper Such neoplasms are usually rapidly fatal or recurring lesions found in adolescents or young adults. Although the term is of recent origin sarcomas of this type have been previously described as *endotheliona* or capsular sarcoma (Ewing) Knox, however in reporting three cases in 1936, credited the first case to Ruediger Rydygier in 1906, and was able to collect only twenty-two examples including the three of her own In 1944, Haagensen and Stout reported 104 cases, with only 3 with five-year survival periods. The recognition of these cases when both clinical and pathologic data are available is not difficult. They occur in the region of joints, (most often the knees) bursae or tendon sheaths, usually in the extremities, but occasionally about the bursae in the pelvic region. The duration of the symptoms varies from several months to a period of several years. Pain swelling and dysfunction of the limb are outstanding features.

The tumor at operation may appear to be encapsulated but is usually attached to or invading tendon or joint capsule. Its texture varies according to the degree of vascularity but is generally soft, white and fleshy It may have hemorrhagic or friable portions. The outstanding microscopic feature is the combination of areas of spindle-cell sarcoma with masses of epithelial-like cells which may assume an alveolar or papillary arrangement. The tendency for the cells to surround small open spaces suggests the normal structure of the synovial membrane and is a distinguishing fea

ture which has led to the separate classification of these neoplasms. In the ten cases in which Knox was able to trace the outcome, only one survived beyond the five-year period, a patient who died with metastasis to the lungs seven and one-half years after amputation of the arm. We reported a similar case in an earlier edition in which tion of symptoms was recorded in 27 cases. In 15 this was an average of three months, and in 12, an average of 6½ years. In three cases, the malignant tumor apparently originated from a pre-existing benign lesion which had been present from 15 to 20 years. In 22 cases adequately followed, only 3 survived the five-year period, but



Fig. 556 Photomicrograph of fibroma shown in Figure 555

the patient died with sarcoma in the interscapular region seven years after a wide excision of a synovial sarcoma of the knee joint. We have followed a second case with a lesion of a toe, dead with widespread metastases to the lungs and brain five years after a primary resection (Fig. 557) Up to 1937 only 14 cases had been studied by one of us (CFG) In the past 10 years, however the total has been increased to 35 Twenty-three of these cases were between the ages of 11 and 39 and 12 between the ages of 40 and 72. Sites affected in the order of their frequency were the knee (17) the foot (4) the ankle (2) the elbow (3) the wrist (2) the thumb (2) the symphysis pubis, pectoral tendon calf thigh and shoulder one each. The dura there are no known cures. With few exceptions, a local excision preceded the radical operation. Amputation or radical resection is the treatment of choice.

Angioma and Lymphangioma of the Tendon Sheaths

Sabrazes and others, in describing 25 cases of angioma in or about the *joints*, mention 9 juxta-articular lesions of angiomatous nature which were not in the joint proper Della Mano reported a case of cavernous hemangioma in a woman aged fifty-one, on the palmar and dorsal surfaces in the tendon sheaths of the left hand, with foci of calcification These were excised and given postoperative roentgenotherapy Prin

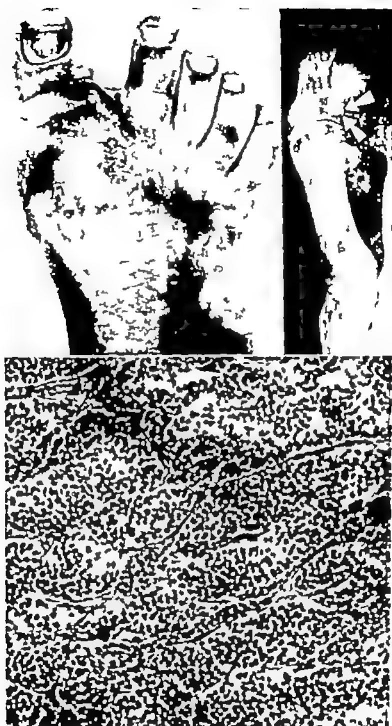


FIG 557 Photograph, roentgenogram and photomicrograph of synovial sarcoma of the foot. The tumor occurred on the right big toe at the metatarsophalangeal joint of a 30-year-old woman. The tumor was treated by intrapedal amputation by Dr Samuel S Hanflig, of Boston, Mass., on Jan. 19 1939 The patient died with metastases to the brain and chest approximately 5 years later without signs of local recurrence The first two toes were removed and the corresponding metatarsal bones. The patient was able to walk with a special shoe.

cigalli also reported an hemangioma in the peroneal tendon of a girl aged 14

Three cases of lymphangioma have been

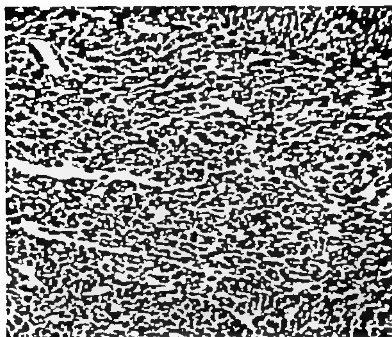


FIG. 558. (No 41836) Cellular synovial sarcoma from the under surface of the quadriceps tendon. The lesion oc curred in a boy aged 16 The roentgenogram showed a def inite tumor shadow raising the tendon and the patella. The tumor was excised in 1928 but recurred, and the leg was amputated in 1929 Following this the patient could not be traced.

reported recently Scagliosi reported a case in a child aged 7 with a bilateral tumor of the tendon of the posterior tibial muscles, external to the malleolus in each foot, which was diagnosed as simple lymphangioma. Huguenin reports two cases, one in the quadriceps tendon of a child and the other in a male with multiple tumors on the hand. No cases of this type were available for study in this laboratory

TUMORS OF THE JOINTS

Tumors of the joint correspond pathologically to those found in the tendon sheath but are more rare Osteochondromatosis of the joint, giving rise to free bodies, parallels the osteochondromatous lesions seen in the tendon sheath. The giant-cell tumors of the joint and xanthomatous lesions with lipoid phagocytosis are not uncommon Fibroma and fibrospindle-cell sarcoma may occur in addition to lipoma and hemangioma. The list of cases in this laboratory is as shown in table 91

Sarcoma invading the joint from the adjoining bone is relatively rare. It occurred

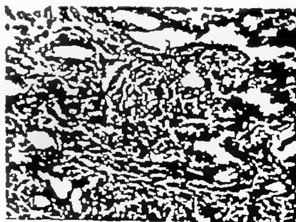


FIG. 559 Photomicrograph of pseudo-epithelial type of synovial sarcoma.

Table 90. Tumors of Joints

Tumor	No.
Osteochondromas or chondromatosis	13
Cartilaginous cysts	2
Giant-cell tumors	3
Xanthomatous giant-cell tumors	5
Lipomas	4
Fibroma and fibrospindle-cell sarcoma (each 1)	2
Hemangioma	1
Total	30

only three times in approximately 1,000 malignant lesions of bone recorded in this laboratory

Razemon and Bizard, in 1931, were able to collect 74 cases of primary tumors of the joint from the literature. Among 45 benign tumors, 26 were in the xanthomatous or giant-cell tumor group Seventeen were angiomas one fibroma and one lipoma were listed. Among 29 malignant tumors, synovial sarcoma with a structure indicating an origin in the synovial membrane predominated. (This is the so-called capsular sarcoma of Ewing) One chondro-



Fig. 560 (No 26286) Cartilaginous tumor of the ankle joint occurring in a laborer of 40 years. The lesion was originally thought to be tuberculous. A resection of the ankle joint was performed in June 1920 The tissue showed islands of newly formed cartilage. In 1921 there was recurrence, with marked destruction of the ankle. Amputation was performed July 1 1921. The patient was reported well in 1924. The roentgenogram shows the marked osseous destruction produced by the recurrent growth. The numerous loose bodies present suggest that the tumor originated in osteochondromatosis of the ankle joint.

sarcoma, two myxosarcomas and one liposarcoma were listed. The histologic types of the remaining sarcomas were not specified. The majority of the malignant tumors recurred or metastasized. One patient with a fibrosarcoma amputated following recurrence was well 27 months later. Twenty five of these sarcomas involved the knee the remainder the ankle. These authors do not include osteochondromatosis with free bodies or cysts of the joint cartilage in their list of tumors.

CARTILAGINOUS TUMORS OF THE JOINTS

In 1924 Jones reviewed the literature on osteochondromatosis with the formation of loose bodies of the joint. Although Ambroise Paré discussed loose cartilage in the joint in 1558, Jones credits Laënnec with the first description. Jones was able to collect 27 well described cases in the literature and to these added 19 others. In 1933 Vincent and Vincent were able to collect 111 cases. In reviewing the literature we have been able to find 15 additional case reports.

Chondromatosis of the joints is found in adults between the ages of 20 and 50 and is more frequently seen in males than females. The joints involved, in the order of frequency are the knee, elbow ankle, hip and shoulder. The disease originates in the capsule and synovial membrane and may also involve the neighboring bursae and tendon sheaths. The symptoms are usually mild and progressive, and the disease is most often monarticular. Glistening, pearly bodies varying in number from a few to more than a hundred are found free or attached to the synovial membrane. Numerous stages in the development of cartilage and bone are found in the free bodies. Jones and also Reimann and Kienböck have reported sarcomatous change in this condition.

These cartilaginous joint lesions are not difficult to diagnose in the roentgenogram. The structures enclosed by the joint capsule show numerous spotted calcareous nodules, while calcareous stippling may extend along the surface of the bones or some distance along the neighboring tendons and into the regional bursae. With invasion the neighboring bones may show rarefaction or increase in density.



FIG. 561 (No 24367) Osteochondromatosis of the knee joint with recurrence and bone invasion. The lesion occurred in a white male, aged 40 years, who had noticed swelling and stiffness of the joint in April 1919 when irradiation was given following an excision. In August 1920 amputation was performed for recurrence. The patient was reported well in 1934.

The condition may be eradicated by removal of the loose bodies and excision of the synovial membrane and bursae containing the cartilaginous masses. Recurrences may be seen, but are not frequent (Figs. 561 and 562).

The modern tendency is to regard chondromatosis as definitely neoplastic, although in the older literature free bodies in the joints of whatever character were

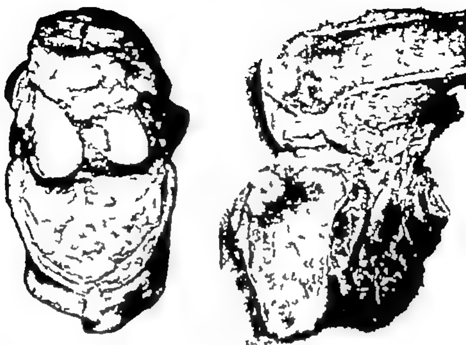


FIG. 562. Gross specimens of the recurrent tumor showing masses of cartilage within the joint and invasion of the tibia, same case as Figure 561

usually placed in a single group The continuity of the various stages of development seen under the microscope in which the growth of the tumors may be traced from mesenchymal cells in the synovial membrane to fetal cartilage, to cartilage, and thence to bone favors the neoplastic theory



FIG 563 *Photomicrograph showing cartilaginous nature of tumor shown in Figure 562.*

In addition to the typical cases of chondromatosis involving knee and elbow recorded in this laboratory there were four cases of recurrent cartilaginous tumors of the joints and juxta-articular structures associated with free bodies. In one of these the lesion was at the ankle, in a patient aged forty Recurrence followed resection of the ankle joint, necessitating amputation. The tumor had invaded the tibia, fibula, and os calcis (Fig 560) A similar condition is recorded in a male aged 40 who had pain in the knee of 2½ years duration (Figs. 561 and 562) Recurrence followed an operation in 1919 in which cartilaginous masses were removed from the joint. Irradiation was tried and amputation was performed for the recurrent growth. The femur and tibia were invaded. Both of these patients have remained well. The other two cases were cartilaginous lesions of the knee joint

of similar character In one a primary amputation was performed and in the other excision was followed by recurrence

EXTRUSION AND CYSTS OF THE JOINTS AND JOINT CARTILAGES

Fibrocartilaginous masses attached to the intervertebral disks which may simulate

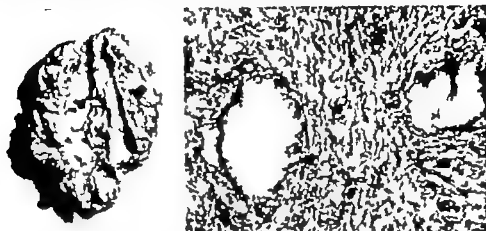


FIG. 564 (No. 40448) Gross specimen and photomicrograph of a lymphangioma of the knee involving the bursal and joint cavities. The lesion had been present since birth, producing a small nodule which was visible just beneath the patella At the age of 5½ years, following a trauma to the knee, the tumor enlarged rapidly and was excised. The gross specimen shows numerous small angiomatous spaces. The photomicrograph shows typical angiomatous spaces filled with coagulated lymph and surrounded by endothelium.

tumors of the spinal cord, have been variously reported as chondromas or enchondromas, extrusion of the disks, loose cartilage and cartilaginous nodes Bucy in 1930 was able to collect 16 cases, 9 cervical, 3 thoracic and 3 lumbar The number of cases treated surgically in the past decade totals in the thousands.

At present this is a well recognized clinical entity known as herniated or protruded intervertebral disk. Nerve root pain or radiculitis, which is aggravated by coughing, sneezing or straining at stool and which follows the distribution of the sciatic nerve or nerves of the brachial plexus is produced by compression of neural fibers by protrusion of a fragment of the intervertebral disk. This is the most frequent etiology of the syndromes formerly known as low back pain, sacro-iliac strain and sciatica. The lumbar portion of the spine is most often affected, over 90 per cent of the recorded cases occuring at the fourth and fifth lumbar interspaces. Involvement of the cervical or thoracic spine is relatively rare. The patient (usually a young adult) leans away from the affected side there is loss of lumbar lordosis, and spasm of the lumbar muscles. Motor weakness, atrophy of the calf muscles or signs of early paraplegia may be present but usually only loss of the Achilles reflex is found.

The spinal column may appear normal in the roentgenogram or there may be narrowing of the interspace. Congenital anomalies of the vertebrae may be present but these are without diagnostic significance. If a lumbar or thoracic lesion is suspected Love believes that a spinogram should be made by the introduction of air or oxygen into the spinal canal If lipiodol is introduced, it should be removed after examination. If paraplegia has not occurred, relief is usually complete following surgical removal of the protruded disk.

The cartilage in these lesions is an adult, hyalinized variety without signs of proliferation or inflammation under the microscope. Instead, it shows fragmentation and

degeneration. In this respect it resembles somewhat the tissue of traumatic joint mice described by König in 1888 in the knee.

The normal intervertebral disk is composed of (1) the nucleus pulposus, (2) the annulus fibrosus, and (3) an upper and lower hyaline cartilaginous plate. The nucleus pulposus is a gelatinous central mass which appears like boiled tapioca. It apparently is under great tension during youth and middle age and bulges when the vertebrae are cut in the midsagittal plane The annulus fibrosus is a tough fibrocartilaginous structure that encases the nucleus pulposus and sends fibers into it. It is thin above and below where it comes in contact with the cartilaginous plates.

Hyndman is of the opinion that trauma may play a role in the extrusion of the nucleus pulposus but that degeneration of the disk is the important predisposing cause. In such degeneration the nucleus pulposus shrinks away from the surrounding annulus fibrosus and appears dehydrated and becomes largely replaced by fibrocartilage from the annulus. The annulus also degenerates and becomes progressively thin so that it is inadequate to retain the sequestrating nucleus and the latter is extruded posteriorly into the spinal canal compressing the nerve root following relatively slight or repeated trauma.



Fig 565 (No 42128) Giant-cell tumor of the ankle joint occurring in a white male aged 27 The patient complained of rheumatic pains in the right ankle of six months duration. There were swelling and tenderness anteriorly Resection of the joint was performed in August 1928 and the patient was reported well in April 1934 The roentgenogram depicts a shadow anterior to the ankle joint eroding the tibia and astragalus.

Cysts. Sixty seven cases of cysts in the articular cartilages of the knee were collected by Marique (1932) who believed that trauma played an etiologic role. The patients were between 15 and 30 years of age. The cysts were 2 to 4 cm. in diameter and usually involved the external meniscus. A few have been found on the internal side, some involving both menisci rarely the lesion is bilateral. Limitation of motion, pain and atrophy of the thigh may occur Careful microscopic studies show that these cysts are due to mucoid regression in the joint cartilage. Bristow and Lord

have given the pathology in detail The cysts form from multiple foci which grad ually coalesce: they may be multilocular at excision

Cysts and Angiomas of the Synovial Membrane

Cysts of the synovial membrane within the joint resulting from mucoid regression may be included. Simple excision usually suffices to case these

One cystic tumor within the synovial membrane proved upon microscopic ex amination to be a lymphangioma and was connected with the bursa surrounding the joint (Fig 564)

Both of the cases of hemangioma of the joints recorded in the present series affect

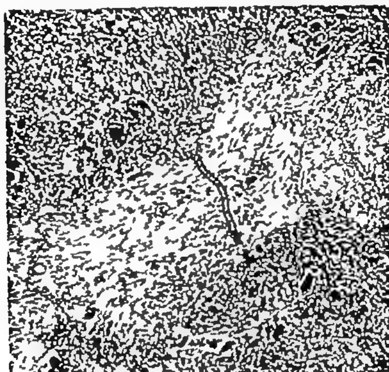


Fig. 566 Photomicrograph of typical benign giant-cell tumor shown in Figure 563 Small islands of new bone for mation and fibrous strands are surrounded by a proliferation of giant cells.

in the connective tissue are similar to those found in the tendon sheath. D Auteuil reviewed the literature on these synovial cysts. They may recur after excision and some are true neoplasms.

Baker's Cysts are bursal cavities formed by mucoid regression in herniated fringes of synovial tissue from the knee joint. The cysts connect with the knee joint by a patent or obliterated fibrous channel. These cystic synovial tumors are filled with a clear or bloodstained mucinous fluid. The fibrous wall may subdivide the cavity with multiple partitions. So-called *rice bodies* ed the knee. They were in young adults who complained of intermittent pain and swelling. The tumor has a characteristic boggy feeling. Occasionally pulsation can be felt. The important feature of these cases is the danger of surgical interven tion, which may result in fatal hemorrhage, and the satisfactory results by irradiation

Giant-cell Tumor, Xanthoma and Synovioma of the Joints

If the cartilaginous tumors of the joints are excepted, the majority of the benign lesions are characterized pathologically by giant-cell proliferation, accumulation of

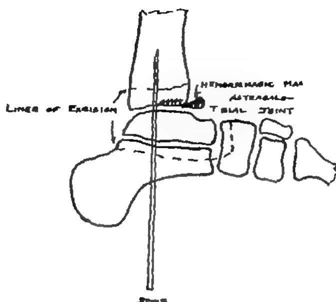


FIG 567 Operative sketch of case shown in Figures 565 and 566 A separate tumor mass (about the size and contour of a sesamoid bone) occupies the astragalo-tibial joint The entire astragalus was removed and the lower end of the tibia was re sected. (Dr F J Gaenslen, Milwaukee Wis.)

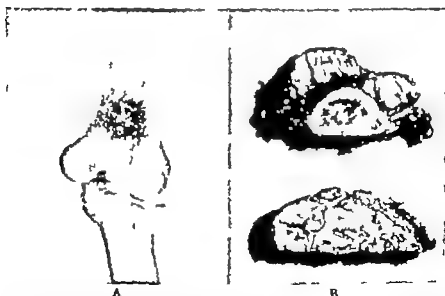


FIG 568 (No 46724) Roentgenogram and gross specimen of a xanthomatous lesion about the elbow joint, occurring in a white male aged 44 The patient, who had been treated for diabetes for six months, complained of pain and swelling about the right elbow The roentgenogram shows a tumor of the soft parts above and below the elbow with invasion of the lower end of the humerus and the olecranon of the ulna. The gross specimen is a lobulated mass characterized by soft yellow tissue invading the joint and involving the periosteum. The specimen was obtained by resection of the joint.

foam cells, and a connective tissue derived from the synovial membrane. Some of these synovial tumors are characteristically of the giant-cell tumor type and show a tendency to involve neighboring bone (Figs. 565 and 566) In a few foam cells predominate, and there is a tendency for the growth to ex tend about the periarticular structures. tissue predominates in a tumor of the large joint, the lesion is malignant. Faulkner following a previous report by Hartman divided the cases into those with and without giant cells. In the report of Razemon and Bizard, 26 of 45 benign tumors of the joints were in the xanthoma or giant-cell group

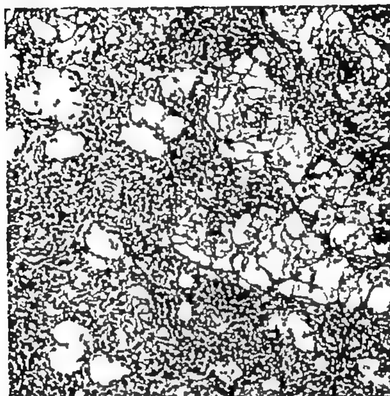


Fig 569 Photomicrograph of xanthomatous tumor shown in Figure 568 showing a stroma of lymphocytes and fibroblasts and many foam cells.

These are obviously of the symptomatic xanthoma type occurring in diabetics or patients with renal symptoms (Fig 568) On the other hand, these lesions may be composed of a loose connective tissue representing a proliferation of the ground substance of the synovial membrane (Figs. 575 and 576) While giant-cell tumors, xanthomas and synoviomas are thus represented, most of the lesions show an intermingling of giant cells, xanthoma cells and synovial tissue. When giant cells predominate, the lesion is usually benign. There were two exceptions. When synovial

Three lesions of a large joint with involvement of bone are classified as giant-cell tumor in this laboratory Two of these occurred in white women aged 21 and 42 years, in the knee joint, and one in a male aged 37 at the ankle The latter invaded both the tibia and the astragalus. In this case a separate mass, the size of an olive, was found anterior to the joint at the site of an aberrant sesamoid bone (Fig 567) Microscopically this lesion showed typical giant-cell tumor tissue invading bone. Of the other two lesions, in the knee joint, one invaded the bone and one the joint carti

lage, although the bulk of the tumor was within the synovial membrane. Microscopically in these two cases xanthoma cells accompanied the proliferation of giant cells. All of these patients have remained well from five to eight years after excision.

Five xanthomatous lesions with numerous foam cells and occasional giant cells are recorded. Four of these were within the knee joint and did not involve the bone or the periarticular structures. Histologically however they graded imperceptibly into the group described above as giant-cell tumors. One typical xanthoma was recorded, at the elbow joint infiltrating the periarticular ligaments and tendons. This was in a diabetic of 44 and is a typical symptomatic xanthomatous lesion, phagocytic rather than neoplastic in character etiologically unrelated to the group of tumors under discussion (Figs. 568 and 569)

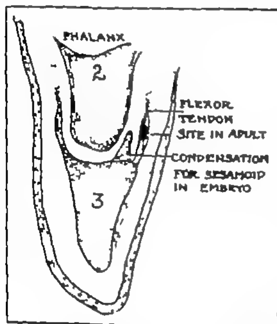


FIG. 570 Sketch of pig embryo (52 mm.) showing the development of the sesamoid bone on the flexor side of the digit. The primordium of the sesamoid is preformed in cartilage from the joint side of the distal phalanx. Later this cartilaginous structure takes up a position within the tendon sheath.

The xanthomatous giant-cell tumors of the joints are histologically similar to the giant-cell tumors of the tendon sheaths described above. The explanation of this similarity is found in the embryology of the sesamoid bones. The original condensation for the future sesamoid bone buds from the joint side of the future bone, just beneath the tendinous attachment. An abortive formation of this sesamoid type undergoing resorption by giant-cell proliferation, may give rise to a xanthomatous giant-cell tumor within the joint (Fig 570) Later when this same embryonic sesamoid focus has migrated to its final position within the tendon sheath, a similar resorption by giant-cell proliferation gives rise to a tumor of the tendon sheath. Whether the tumor is of tendon sheath or synovial origin, the typical fibrocartilaginous structure of the sesamoid bone may be found at times remaining in the tumor (Fig 571)

Lipoma, Fibroma and Fibrosarcoma (Synovial Sarcoma) of the Joints

Hypertrophic fringes of synovial tissue distended by fat are frequently observed with arthritic changes. True articular lipomas are uncommon, however Four cases are recorded in this laboratory (Fig 572) We have been able to find only 5 isolated cases reported in the literature (Neugebauer Driels (3) Razemon and Bizard) All of our cases were located at the knee joint. Driel's three cases occurred in the ankles of adipose women. The tumors are accompanied by fluid in the joint, which is relieved by excision of the growth.

Razemon and Bizard recorded nine spindle-cell sarcomas of the joint in 1931. These tumors, which involved the synovial membrane, also invaded the neighboring periarticular structures. From the modern point of view they would be regarded as cellular synovial sarcomas, and their distinction from similar tumors arising near the joints from the bursae and tendon sheaths is not relevant. In our experience, the cellular synovial sarcomas, particularly in

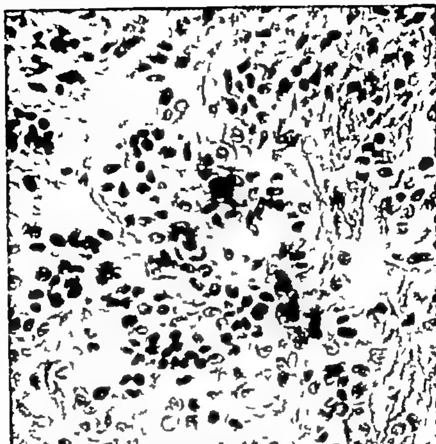


FIG. 571. (No. 42995) Photomicrograph of a giant-cell xanthoma of the tendon sheath. The intercellular substance is composed of fibrocartilage from which the sesamoid bones are derived.

young adults, are the most likely tumors of the synovial group to invade the joint proper Their pathology and clinical behavior have been discussed above under synovial sarcoma of the tendon sheath.

Synovial sarcoma confined to the joint cavity or to the synovial membrane appears to be excessively rare. One case of verified synovial sarcoma in our series occurred in an adult female and invaded the synovial membrane of the knee joint and the bursal cavity beneath the patella (Figs. 574, 575 and 576) The tumor was treated by wide excision Microscopically it retained its synovial structure. A follow-up report on this case seven years later stated that the knee had remained well for more than five years, when the patient developed sarcoma of the interscapular region from which she died. It has not been possible to ascertain if this growth was metastatic.



FIG. 572. (No 3383) Arborescent lipoma from the knee joint.

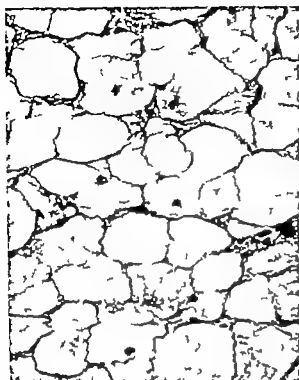


FIG. 573. (No 52502) Photomicrograph of a xantholipoma of the knee joint.



FIG. 574 (No. 39726) Synovial sarcoma of the knee with invasion of the bursal and joint cavities, showing the lobulated character of the growth. The patient remained well for five years after excision. Following this, a metastasis developed in the interscapular region, which proved fatal.

DIFFERENTIAL DIAGNOSIS

A variety of arthritic disturbances, including forms of arthritis, fibrositis and other rheumatoid conditions, may at times simulate neoplastic involvement of the joints, the tendon sheaths or the bursae. As a rule, the arthritic and rheumatoid conditions affect multiple joints or produce systemic reactions of fever weakness or changes in the blood picture which aid in distinguishing them from neoplasms. The symptoms referable to the joint also vary in intensity and are characterized by exacerbations and remissions. When roentgen changes are demonstrable in the bones about the affected joint, the bones on both sides of the joint are involved, which is rare for malignant neoplasms of the bone or joints. However care must be exercised in distinguishing bone atrophy of disuse from the erosion which occurs with tumor formation. For purposes of ready reference, a brief summary of the arthropathies is given in the following paragraphs.

1 **Rheumatoid Arthritis.** This is a subacute and chronic inflammation, of unknown etiology involving multiple joints in young adults. It is characterized by pain, anemia, fever lymphadenopathy and an increased blood-sedimentation rate. At first, only one or several joints are attacked, those first affected usually include the phalangeal joints of the hands. During the acute attack, the involved joints are swollen, red, hot and tender The phalangeal joints have a characteristic spindle-shaped enlargement. There are fusiform thickenings about the joints with atrophy of the bones. Erosions of articular surfaces with punched-out areas finally supervene. Fibrous adhesions may bind together such opposing, eroded, articular surfaces. There are contractures, subluxations and ankylosis late in the disease. The end stages are often characterized by severe crippling

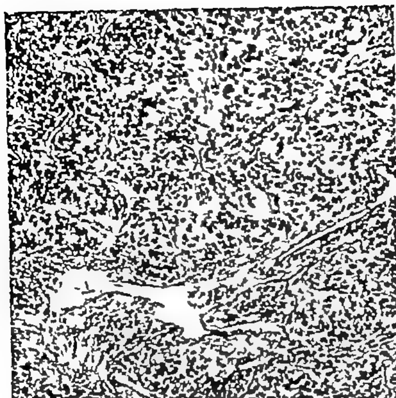


FIG. 575 Low-power photomicrograph of synovial sarcoma of knee joint shown in Figure 576 showing synovial like arrangement of fibroblasts.

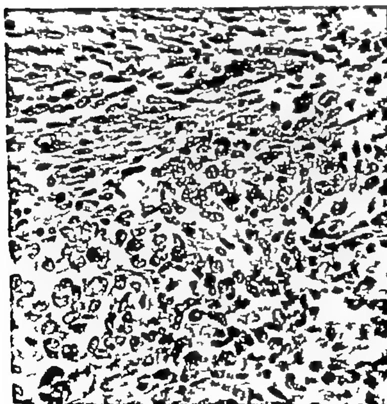


FIG 576 High-power photomicrograph of synovial sarcoma shown in Figure 575

2. Ankylosing Spondylitis (Marie-Strümpell disease) This disease is a spinal arthritis of the rheumatoid type usually in young male adults. It progresses over many years, producing narrowing of the articular cartilages, decalcification of the vertebrae and ossification of the spinal ligaments. It eventually produces complete fixation of the spine. This form begins in the lumbosacral region and progresses upward. The Bechterew variety begins in the cervical region and progresses downward. The onset is characterized by pain, but in between repeated exacerbations there may be long periods of remission.

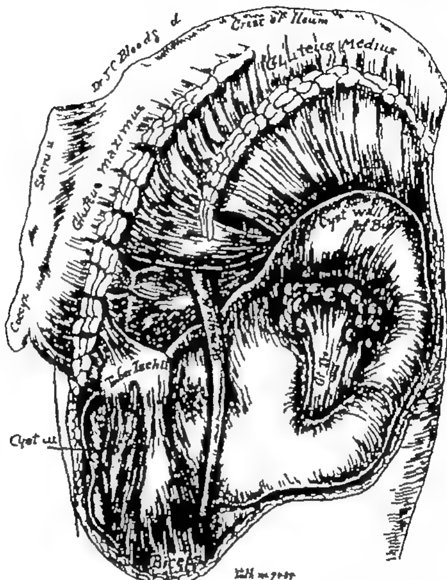


Fig. 577 (No 7484) Large bursal sac over the greater trochanter containing osteochondromatous masses and calcified material. This so-called exostosis bursata may be of neoplastic origin. Some of them have undoubtedly been calcinosis universalis with secondary deposits in the bursae.

3. Septic Arthritis. Pyogenic organisms invading the joint produce septic necrosis with ultimate ankylosis unless promptly healed by antibiotic therapy The offending organisms are gonococcus, streptococcus,

pneumococcus, etc. The synovial membranes are the seat of suppurating inflammation and the joint fluid acts as a culture medium for the organisms. The septic arthritis may be part of a generalized septicemia, which may be complicated by bacterial endocarditis.

4 **Osteoarthritis.** This is a chronic degenerative disease found usually after the age of 45 In women it often follows the menopause There is "lipping" on the margin of the articular surfaces due to the formation of osteophytes. The central portions of the articular cartilage degenerates, but fibro-osseous and osteochondral tissue proliferates at the margin The symptoms are relatively slight unless injury or infection exacerbates the condition. Obesity and heredity are contributing factors. The terminal phalangeal joint may have juxta articular nodules known as Heberden's nodes. These may at times develop acutely and contain gelatinous material like a ganglion

5 **Gout** Gout occurs predominantly in males after the fortieth year The blood uric acid is usually elevated, or rises just before attacks. The disease is present in many generations in the same family and is independent of dietary habits. The attacks last from one to two weeks and become polyarticular and febrile. The attacks are sudden in onset and severe. After several or more attacks have occurred osseous changes are produced by tophi deposited subchondrally which produce multiple small, punched-out zones in the ends of the bones about the phalangeal joints, elbow knee, etc. The attacks are suppressed by colchicine therapy and the pain relieved by salicylates. Some individuals have repeated attacks over many years without demonstrable residual findings.

6. **Pulmonary Osteoarthropathy** This occurs with bronchiectasis, lung abscess, empyema or tuberculosis. In fully developed cases, thick subperiosteal layers of new bone are seen in the osseous structures of the tarsus, carpus, forearms and legs. The new bone is coarse—then later dense—and is deposited distally suggesting anoxia as the cause. Clubbing of the fingers is an independent soft tissue reaction There is round-cell infiltration of the synovial membranes and necrosis of the joint cartilage

7 **Brucellar Arthritis** In the acute flare-ups of brucellosis a number of patients have transient effusion in the joints. Agglutination tests establish the diagnosis. With progress of the disease, a few have definite destructive lesions. The joint surfaces are narrowed and the underlying bone is sclerosed. There may be exacerbation but the tendency is toward healing

8 **Psoriatic Arthritis.** This occurs in the fourth to sixth years of psoriasis, and is like rheumatoid arthritis with a predilection for terminal phalangeal joints.

9 **Neuropathic Arthropathy—Charcot's Joint** This is a disintegration of the joints and the extremity of the articulating bones secondary to loss of proprioceptive sense consequent to central nervous system disease (tabes dorsalis, leprosy syringomyelia) The diseased joint suffers effusion then, destruction of the joint cartilages, eburnation of the bones and finally ossification occurs in periarticular structures. There is a scattering of osseous and cartilaginous debris. The condition is relatively painless. The motion about the joint is increased and swelling is usually pronounced. The roentgen findings demonstrate a variety of osseous and articular changes.

10 **Hemophilia.** Hemo-arthrosis occurs in blood dyscrasias with hemorrhagic tendencies such as hemophilia and purpura. The hemorrhage into the joint produces swelling and haziness on roentgenographic examination. Later there is ossification of ligaments and joint mice may form. The end results may be ossifying hematomata with ankylosis of the joint.

11. **Allergic and Postinfectious Arthritis** This is a relatively frequent form of arthritis associated with so-called serum sickness or with collagen necrosis which accompanies such postinfectious diseases as rheumatic fever lupus erythematosis and

polyarteritis. Most observers believe that the joint disturbance is part of an allergic reaction of nonspecific etiology

12. **Palindromic Arthritis.** This is a chronic, recurrent, serous arthritis of unknown cause. The attacks are usually polyarticular and are accompanied by swollen tender hot joints. The cute attack subsides without residuum.

13. **Intermittent Hydrops of the Knee Joint** This is a serous bursitis with or without arthritis of the knee joint, occurring in young adults. It comes on in successive attacks accompanied by fluid transudation into the articular or periarticular spaces. The attacks are transient and accompanied by a moderate degree of pain. They subside without trace but tend to become more frequent and more chronic.

14. **Bursitis.** Bursitis may be the result of chronic trauma, such as "housemaid's knee" or "tennis elbow Such a bursitis over the proximal joint of the big toe is called a bunion. It is a chronic, nonsuppurative process. The bursae may sometimes be involved in septic processes, but this is relatively rare Bursitis may complicate rheumatoid arthritis or gout. A chronic form of bursitis associated with fibrositis occurs in the subdeltoid bursa and is known as Codman's shoulder The fibrositis involves the adjoining tendons, which may undergo calcification The upper end of the humerus may show atrophy Fibrositis tends to be persistent and unusually chronic, but symptoms sometimes yield to local injections of novacaine. Point tenderness may be traced over the greater tuberosity of the humerus or over the coracoid process. Usually pain is provoked by putting the arm behind the head.



FIG. 578. (No. 40450) Recurrent chondromyxoma of the popliteal bursa The photomicrograph shows fetal cartilage cells embedded in precartilaginous connective tissue

15 **Fibrositis.** Fibrositis is a nonsuppurative inflammation of the fibrous supporting tissues, most commonly of the sheaths of

muscles or deep fascial layers. This concept of the origin of local rheumatoid pain supplants the older concepts of lumbago chronic nonspecific myositis, muscular rheumatism and periarthritis. It is most common *in young* adults and men are affected three times as frequently as women Affection of the lumbar fascia (lumbago) is more common in men and a subcutaneous fibrositis more common in women

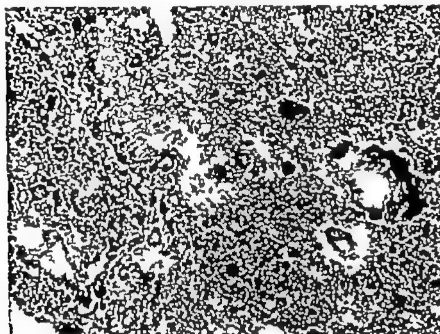


FIG. 579 (No 15337) Calcinosis universalis with deposits in the bursae. The photomicrograph shows calcareous deposits, giant cells, and much amorphous material. The patient died with pathologic calcification of the kidneys after the appearance of numerous recurrent tumors in the bursae overlying the hip and shoulder joints.

The condition is accompanied by pain, tenderness, muscle spasm, fibrous nodularity and disability without systemic manifestations. The etiologic factors are trauma, focal infection and prolonged muscular strain in heavy industry It may complicate rheumatoid arthritis, gout and other toxic states. The pain is usually improved after exercise and worse after rest. The absence of effusion in the joints and the absence of muscle atrophy or ankylosis are important in differential diagnosis. Novocaine injections afford relief

16 Sacro-iliac Strain. This is really an acute fibrositis of the sacro-iliac ligaments. Many of the cases included in the old concept of sacro-iliac strain or sciatica are in reality the result of a protruded intervertebral disk in the lower lumbar region

TUMORS OF THE BURSAE

Tumors of the bursae are rare and are clinically distinguished with difficulty from inflammatory or traumatic lesions in these structures. Unless adequate dissection is performed, the bursal origin of the lesion is difficult to demonstrate. Osteochondromas, chondromatous and myxomatous (chondrosarcoma) tumors of these structures do occur however and have been described in the literature Fibrosarcoma of the synovial sarcoma type and endothelial sarcoma) have also been reported. One of the earliest and best contributions on tumors of the bursae is that by Adrian who collected 19 cases. Schwamm has reviewed the litera



FIG. 580 (No 39964) Synovial sarcoma of the bursa overlying the trochanter of the femur The patient was a white man aged 26 who had a tumor the size of a grapefruit in the upper third of the thigh. Operation was performed in December 1927 A large encapsulated tumor mass was found resting upon the trochanter of the femur The cut section of the tumor showed numerous gelatinous and calcareous areas. Death occurred in July 1932, with metastases to the lungs



FIG 581. Photomicrograph of tumor shown in Figure 580 showing calcareous areas.

ture collecting five additional cases and adding one of his own. In the present series, five tumors are recorded, bringing the total to thirty

Bursal neoplasms parallel in character those of the tendon sheaths and joints. One osteochondroma and two benign chondromas are recorded in the literature. The majority of cases published show a cartilaginous structure which is myxomatous and definitely malignant. Our own cases, including two osteochondromas and two chondromatous lesions and the reports studied indicate that bursal tumors composed largely of cartilage are prone to recur and to undergo malignant change. These lesions are usually found about the knee joint, at the site of the prepatellar bursa, but may occur on the popliteal side of the joint. One of the cases studied in our series in the popliteal region is illustrated in Figure 578 and described in the accompanying legend. An osteochondromatous tumor in the bursal sac over the greater trochanter is also shown (Fig. 577) When undergoing malignant change these chondromatous lesions become pseudo-fluctuant and contain large amounts of myxomatous material in addition to cartilage. Their histology demonstrates the precartilaginous nature of the tissues forming the bursae.

No verified case of giant-cell tumor in a bursa was found. One case studied (Fig 579) was originally observed in a child of ten who had a subdeltoid mass excised

which was microscopically diagnosed as giant-cell tumor or xanthoma. Many small calcified bodies were present. In the next ten years numerous bursal tumors appeared in the extremities and the patient eventually came to autopsy with pathologic calcification of the kidneys. These calcareous lesions with giant cells described as xanthomas of the bursae have since been demonstrated to be calcinosis universalis with deposition of calcified masses in the bursal sacs. They are akin to the periarticular deposits of uric acid observed in gout. A similar case is cited by Adrian as being reported by Milian and Neveu. This case occurred in a woman of 39 and the lesion was in the prepatellar bursa. Microscopically the authors could find no tumor tissue and termed the condition a calcareous granuloma.

Cystic tumors of the bursae probably occur but they are difficult to distinguish from simple fluid distention of these structures following chronic irritation and trauma. In the older literature they are sometimes referred to as cystic hygroma.

Fibrospindle-cell sarcomas, now called synovial sarcoma, have been described in the bursae. The majority of these lesions grow slowly and have a tendency to recur locally and to ultimately metastasize. The very cellular growths contain small dilated spaces and large oval nuclei characteristic of synovial tissue. Two cases are illustrated in Figures 580 through 583.

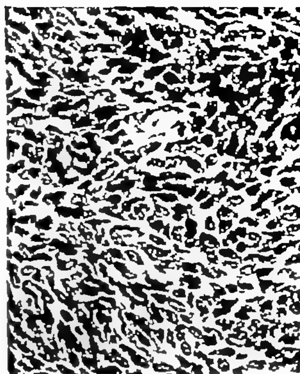


FIG. 582. Photomicrograph of tumor shown in Figure 581 showing histology of synovial sarcoma.



FIG. 583. Roentgenograms of the knee joint and chest in a case of synovial sarcoma. There is a large soft-part shadow in the popliteal space representing a tumor mass the size of a grapefruit. There is no involvement of the underling bone. The lungs are riddled with metastases of the "cotton-ball" type.

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25

Tumors of the Spine

Tumors of the spine present a number of peculiarities because of the close relationship of this portion of the skeleton to the nervous system and because of the persistence of a primitive skeletal tissue, the notochord. In all, there were 291 tumors studied by us in this series. All of them affected bone or were demonstrable roentgenologically. They included metastatic carcinoma, primary tumors of the spinal column (mainly of osseous origin), glial tumors and tumors of the neural sheath of the spinal cord, tumors of generalized distribution (such as multiple myeloma), tumors of the sympathetic nervous system and tumors of teratologic and notochordal origin. These types of tumors are mentioned in the order of their frequency.

METASTATIC CARCINOMA

Metastatic carcinoma was by far the most frequent neoplastic lesion of the vertebral column. Of 291 spinal tumors, 172 (59.1 per cent) were metastatic carcinomas. Schlesinger and Frazier, the former obtaining his data from autopsies and the latter from surgical specimens, pointed out the marked frequency of metastatic lesions of the spine. In adults, such lesions must be considered in the differential diagnosis of any tumor affecting the vertebral column. Table 91 lists the sites of origin of the 172 tumors.

Schlesinger in 13,500 autopsies found 59 metastatic carcinomas of the spine (Table 92).

These two tables present notable differences. Prostatic carcinoma is probably not as frequent as is indicated by the figures in Table 91, since these figures include all the patients with prostatic cancer from the Brady Urological Institute. It will also be noted that cancer of the female genital tract is not listed in Table 91. Behney has shown that of 55 carcinomas of the uterine cervix which metastasized, 5 involved the lower lumbar vertebrae. This should make the condition a frequent source of metastasis to the spine. These and other discrepancies in the two tables are explained by the different methods by which the material was collected. Table 92 undoubtedly shows more nearly the correct incidence.

Carcinoma of the breast may be considered the most frequent cause of metastases to the vertebrae In a series of 100 carcinomas of the breast metastasizing to bone 60 of the tumors were found to be in the spine.

TABLE 91 SITE OF ORIGIN OF METASTATIC CARCINOMAS OF THE SPINE OBSERVED IN SURGICAL PATHOLOGY

Site of Origin	Number of Cases
Prostate	86
Breast	60
Undetermined	14
Gastro-intestinal tract	5
Kidney	4
Thyroid	1
Lung	1
Nasopharynx	1
Total	172

The condition has no predilection for any particular part of the spine and is usually an osteolytic process, though osteosclerosis may be produced. The site of origin at times is not easily detected. The tumor may

TABLE 92 SITE OF ORIGIN OF METASTATIC CARCINOMAS OF THE SPINE OBSERVED AT AUTOPSY (SCHLESINGER'S SERIES)

Site of Origin	Number of Cases	Site of Origin	Number of Cases
Mammary gland	10	Bladder	1
Esophagus	9	Ovary	1
Thyroid	9	Sigmoid	1
Uterus	6	Rectum	1
Bronchus	5	Kidney	1
Stomach	4	Adrenals	1
Prostate	3	Larynx	1
Gallbladder	2	Pancreas	1
Sinus piriformis	2	Origin not given	1
Total			59

be small and may pass unnoticed, or as is so often the case, the carcinomatous breast may have been amputated years before. In one case an interval of 14 years elapsed between the amputation of the breast and the appearance of metastasis in the spine.

Carcinoma of the prostate is more characteristic in its metastasis to bone. In 134 cases it involved the spine in 86 and showed a marked tendency to appear in the sacral and the lumbar vertebrae. It produces a lesion which is predominantly osteosclerotic. One patient lived 3½ years after the recognition of the metastasis. The primary focus of the cancer may occasionally remain undiscovered until postmortem examination In prostatic carcinoma the acid phosphatase of the serum is increased.

In the diagnosis of metastatic carcinoma of the spine it must be remembered that in most cases the lesions are multiple. A solitary lesion occurred in only 25 per cent of cancers of the breast metastasizing to bone. Consequently roentgen examination of the entire skeleton is often necessary A careful search for a primary focus must be made, the most important sites being the breast, the prostate, the cervix, the thyroid, the esophagus and the lung As may be seen in Table 91 a large number of carcinomas of undetermined origin are encountered. As regards the roentgenologic picture, the tendency of metastatic carcinoma of the prostate to cause osteosclerosis is the only consistently recognizable feature.

TREATMENT

Roentgen irradiation of the affected area, rest and sometimes operative relief of compression of the spinal cord are indicated. The affected part of the spine should be protected by immobilization or by hyperextension. Life is often greatly prolonged by roentgen therapy and pain may be controlled. Castration and estrogen therapy is beneficial in cases of prostactic carcinoma with skeletal involvement, and sterilization followed by testosterone therapy is beneficial in mammary carcinoma with osseous spread.

TUMORS OF GENERALIZED DISTRIBUTION

Generalized neoplastic diseases must be considered in conjunction with metastatic



FIG. 584 Roentgenogram of metastic prostatic carcinoma producing osteosclerosis of the spine.



FIG. 585 Multiple myeloma of the spine The twelfth thoracic vertebra is destroyed, and the first lumbar vertebra is rarefied. The lumbar spine is displaced laterally

carcinoma, since the most important representative of this group, multiple myeloma, is easily confused with spinal metastasis.

Among 30 cases of multiple myeloma there were 14 with leading symptoms involving the spine. Multiple myeloma is a tumor of adult life, the period of its greatest incidence being the sixth decade. The pain in 70 per cent of the cases begins in the lumbar and in the sacral region. In 40 per cent of the cases compression of the spinal cord develops.

The roentgenogram is often diagnostic. The lesions are rarefied, punched-out areas and commonly produce pathologic fracture. They are multiple or become multiple in more than 95 per cent of the cases. At times the punched-out areas may be seen in the vertebrae, but more often there is a pathologic fracture (Fig. 585) Sacral lesions show the characteristic defects in the roentgenogram.

Because of the age at which its onset occurs and the multiplicity of its lesions, multiple myeloma is difficult to distinguish from metastatic carcinoma. The following points are useful Metastatic carcinoma is by far the more common. The roentgen picture of multiple myeloma is the more distinctive. Bence-Jones bodies in the urine favor a diagnosis of multiple myeloma, though they may or may not be present with either condition. The presence of chronic nephritis, with nitrogen retention and high serum proteins, suggests a diagnosis of multiple myeloma. Sternal puncture and/or surgical biopsy are definite steps in making the diagnosis. Roentgen therapy is the treatment of choice for both conditions. The lesions of multiple myeloma respond more rapidly than do those of metastatic carcinoma.

Hodgkin's granuloma, lymphosarcoma,

myeloid tumors and the xanthomatous lesions were found in our series of spinal tumors. Craver and Copeland reported osseous changes in 15.7 per cent of 172 cases of Hodgkin's disease. Vertebral changes are said to be most frequent in cases with skeletal involvement, and these lesions may be either osteolytic or osteosclerosing. Neurologic symptoms are common. High-voltage roentgen therapy causes remission of the symptoms, but permanent cure is not established.

There was a single instance of lymphosarcoma with spinal involvement in the present series. Craver and Copeland found that bone was involved in 10.4 per cent of 164 cases. They found that the spine was the most frequent site and that either an osteolytic or an osteosclerotic process may be present. As with Hodgkin's granuloma, compression of the spinal cord may develop. The tumor is radiosensitive.

Myeloid and lymphoid leukemia may occasionally produce changes in bone. The osseous changes associated with chloroma are prominent but we found no instance of such involvement of the spine. Porosity and trabeculation of bone occur in erythroblastosis, and in the vertebral bodies these trabeculations tend to be vertical. One such case was included in this series.

Hand-Schüller-Christian's disease produces circular osseous defects, usually multiple but occasionally single. The skull and the flat bones are most often affected. When a vertebral body is involved, collapse of that body occurs. We had one such case. Anspach reported a case (the patient being a 5-year-old boy) in which the body of the tenth thoracic vertebra was involved. Triangular collapse of this body occurred, but with clear-cut edges, which distinguished the condition from tuberculosis. With irradiation the lesions of the bone heal in most instances.

The one common feature of these neoplasms of generalized distribution, which include multiple myeloma, malignant lymphoma, leukemia, chloroma and xanthomatosis, is the extreme radiosensitivity of the lesion.

BENIGN PRIMARY TUMORS OF THE VERTEBRAL COLUMN

The second largest group of spinal tumors is composed of primary tumors of the vertebral column, which numbered 58 in this series. The relative frequency of the various tumors is listed in Table 93. In all, there were 37 benign and 21 malignant lesions. Among benign tumors the most common are giant-cell tumor (in which type benign bone cysts may be included) and osteochondroma. This corresponds to the relative incidence of these tumors in the remainder of the skeleton.

TABLE 93 PRIMARY TUMORS OF THE VERTEBRAL COLUMN

Types of Tumor	Number of Cases
Benign	
Giant-cell tumor	15
Osteochondroma	10
Bone cysts	7
Chondroma	3
Hemangioma	2
Malignant	
Osteogenic sarcoma	
Chondrosarcoma	8
Osteolytic sarcoma	4
Sclerosing sarcoma	4
Chordoma	5
Benign	37
Malignant	21
Total	58

GIANT-CELL TUMORS OF THE SPINE

There were 15 giant-cell tumors in the present series. In 1935 Murphy collected 45 from the literature and pointed out that the typical history is characterized by injury to the spine in a young adult, followed by pain, tumor and occasionally kyphosis. Symptoms of pressure on the spinal cord may develop. Most of the patients were



FIG 586 Giant-cell tumor of the spine The roentgenogram shows extensive rarefaction of the third and fourth lumbar vertebrae

young adults One girl was 7 years of age and one man 62. The ratio of the males to females is in the proportion of 9 to 5

Eight patients complained only of pain in the back. In five instances, the pain was followed by compression of the spinal cord. In one case the only symptoms were those of pressure on the spinal cord, and in the remaining case the symptoms of this compression preceded the pain in the back. In six cases a mass was present. The symptoms and signs depend, of course, on the portion of the vertebra which is involved and on the direction taken by the tumor in its growth.

The roentgenologic picture is variable but often diagnostic. As with tumors of the long bones, the other lesions with which giant-cell tumor may be confused are hemangioma of the bone and chondroma. Chondroma usually may be excluded because it is rare except in the sacrum Hemangioma has the appearance of giant cell tumor when the neural arch or its processes are involved, hemangioma of the vertebral body however has a very characteristic striated appearance.

Giant-cell tumor may affect any portion of a vertebra, but in our cases it involved the neural arch or its appendages more frequently than it involved the vertebral body Lewis also found this to be true in the cases he reviewed. Only one tumor occurred in the cervical region. The tumors occurred with equal frequency in the other regions of the spine. The roentgenogram may show a rarefied lesion which reduces the portion of bone involved to a barely visible shadow (Fig 588) In the sacrum the margins are usually clear cut and the lesion larger The trabeculations characteristic of giant-cell tumor in long bones may be present and may indicate a healing reaction The typical expansile, trabeculated type of tumor is best seen when the lesion involves a transverse or a spinous process. A tumor of the neural arch may grow into the spinal canal and may be very difficult to detect by roentgen examination. Giant cell tumor involving the body of a vertebra is very likely to cause destruction with collapse (Fig 586) Clear-cut concave edges can be seen

Giant-cell tumor of the spine, in spite of its benign character may cause death. Of the 14 patients, 9 recovered. The causes of death in 3 cases were damage to the spinal cord, invasion of the inferior vena cava and hemorrhage. In 1 case, the tumor had infiltrated the soft parts extensively at the time the patient was last seen. In the remaining case, the patient died from another cause before the giant-cell tumor had healed.

Giant-cell tumor may be diagnosed from the roentgenograms and treated with roentgen irradiation. In some cases operative procedures are necessary in order to relieve compression of the spinal cord or to stabilize the spinal column and prevent compression. An "aspiration biopsy" can be done and is not contraindicated in doubtful cases.

Bone Cysts

In view of the relative frequency of giant-cell tumor of the spine, one would expect bone cysts to be more common in this location. This, however was not observed Multiple involvement of the spine, with bone atrophy and cyst formation, occurs as part of hyperparathyroidism with generalized osteitis fibrosa There were five instances of such lesions. In two of these cystic lesions of the spine complicated the generalized skeletal deformity In both of these cases pain in the back, of increasing severity was followed by signs of cord compression The roentgenologic picture showed diffuse atrophy of bone, bending deformities of the spine (most commonly kyphosis and scoliosis) and rarefaction and expansion of the bodies of one or more vertebrae or of a portion of the neural arch. In three cases of generalized osteitis fibrosa, demineralization and bending deformity of the spine were not accompanied by cysts.

No histologically verified solitary bone cysts of the spine, such as are found in the shaft of the long bones in children, were recorded in this series. There was one such cyst occurring at the sacro-iliac joint. In another instance, a patient had been previously operated on for benign giant-cell tumor and at a second operation a similar lesion which had undergone cystic change was found above the original site. Microscopically this appeared to be a giant-cell variant of the bone cyst. The absence of typical bone cysts in association with tumors of the spinal column lends support to the opinion that the usual bone cyst of the long bones is a benign giant-cell tumor which has undergone healing The failure of such a healing reaction to follow giant cell tumors of the vertebrae is explained by the cancellous structure of the vertebrae and by the absence of a well-defined cortex of compact bone. The less rapidly growing giant-cell tumors may take on a histologic character which justifies their classification as giant-cell variants of the bone cyst, but active giant-cell tumor tissue is the rule.



Fig. 587 Osteochondroma involving the transverse process of the third lumbar vertebra. The tumor is well circumscribed and outlined by calcified cartilage.

Osteochondroma

Benign exostoses, which are so common in the remainder of the skeleton, are next in frequency There were 10 of these in this series. Two were multiple exostoses affecting the remainder of the skeleton as well the other 8 were all solitary lesions. With 2 exceptions the tumors arose from the neural arch or from one of its processes. In 3 cases the tumor projected into the spinal canal and gave rise to the symptoms of compression of the spinal cord.

The roentgenologic picture is typical of osteochondromas elsewhere. The more cartilaginous tumors may be confused with giant-cell tumor Such a condition is shown in Figure 587 This tumor was irradiated and cartilaginous tissue was apparently replaced by bone One of the 10 patients died



FIG. 588 Chondroma of the sacrum The roentgenogram shows a chondroma lesion of nine years duration The tumor has extended into the pelvis and is undergoing calcification.



FIG 589 Chondroma of the sacrum. The roentgenogram shows a circumscribed tumor which is largely radiolucent, but outlined with calcareous stippling

as a result of damage to the spinal cord. Excision is required only for those tumors presenting symptoms.

There was in the series one nucleus pulposus protruding into the spinal canal. This nucleus pulposus had become calcified and was shown in the roentgenogram as a dense rounded mass 1.5 cm. in diameter Compere and Keyes mentioned calcification of the extruded nucleus pulposus in their studies on ruptured intervertebral disk.

CHONDROMA

Camp, Adson and Shagrue stated that chondroma of the spinal column is rare. In this series there are three chondromas which have microscopic confirmation. One patient was under treatment with roentgen therapy for nine years. During this time the tumor showed an increase in size. Chondromas are radioresistant lesions, but grow slowly

HEMANGIOMA

Bucy and Capp pointed out that when the vertebral bodies are involved by angiomatous growths, vertical striations are produced which form an easily recognized roentgenologic picture. When a hemangioma involves a flat bone, such as the sacrum a marked sun ray effect is produced in the periosteal zone. This periosteal reaction is so marked and so regular that it may be distinguished from the somewhat similar picture of sclerosing osteogenic sarcoma in the same region. They also pointed out that the affected bone does not collapse and produce pain but that the first symptoms are those of compression of the spinal cord. One tumor of our series affected the laminas the other the transverse process.

The roentgen picture showed an expansile, trabeculated tumor resembling giant cell tumor (emphasizing the variability of the roentgen picture produced by hemangiomas involving the vertebral column) The histologic picture is almost invariably that of cavernous angioma, and the tumor responds readily to irradiation Laminectomy of course, is indicated when there are signs of compression of the spinal cord.

The small number of hemangiomas of



FIG. 590 Chondrosarcoma of the upper thoracic spine, with multiple involvement of the vertebrae. The roentgenogram is characterized by spotty paravertebral shadows.



FIG. 591 Sclerosing osteogenic sarcoma of the sacrum. The roentgenogram shows the sclerosing tumor overlapping the ilium, with radiating spicules extending alongside the fifth lumbar vertebra.

bone diagnosed is not a true indication of their frequency but indicates how infrequently symptoms are produced. Topfer in 2,154 autopsies found hemangiomas of the vertebral bodies in 257 instances (11.4 per cent) there were multiple growths in 34.

Only one angioma arising outside the spine and producing osseous changes was found. It arose in connection with the dura. The roentgenogram was reported as showing "a bulging of the bony framework of the cervical spinal canal." At operation an extradural hemangioma was disclosed which caused the laminas on the left side to bulge laterally and dorsally

MALIGNANT PRIMARY TUMORS OF THE SPINAL COLUMN

Malignant primary tumors of the spinal column are less common than benign growths. There are but two types osteogenic sarcoma and chordoma. Osteogenic sarcoma includes chondrosarcoma and the osteolytic and sclerosing types of sarcoma.

CHONDROSARCOMA

There were eight cases of chondrosarcoma of the spine. In three the tumor was single and primary in two the growths were multiple but behaved like primary tumors and in the remaining cases the sarcomatous change occurred in multiple exostoses (two cases) or in Paget's disease (one case) Excluding consideration of the time of appearance of the secondary chondrosarcoma, the average age of the patient at the onset was approximately 25 years. In two cases the only symptom was pain in the back, in three pain in the back was followed by symptoms of pressure on the spinal cord, in one these symptoms preceded the pain in the back. Death occurred from three months to three years after the onset. One patient is living seven years after the onset. The tumor is growing slowly at the present time.

In one case an autopsy was performed and multiple cartilaginous tumors were found affecting almost the entire skeleton. At autopsy multiple masses extended along the lateral and anterior portions of the

spine It is probable that a roentgenogram in this case would have simulated that illustrated in Figure 590. These cases are peculiar in that multiple tumors arose simultaneously and were apparently not secondary changes occurring in preexisting multiple exostoses.

Osteogenic Sarcoma

Four osteolytic sarcomas and four sclerosing sarcomas are included in the present series. Two sarcomas of the ostelytic type were superimposed on Paget's disease. The outsanding symptoms were those of pain in the back or pain at the nerve roots, which was frequently followed by compression of the spinal cord. All of the sarcomas terminated fatally with an average duration of life of 21 months. With the exception of the tumor in one case of Paget's disease, in which the sarcomatous change extended throughout the length of the spine, all the growths arose in the sacrum or in the lumbar vertebrae.

Figure 591 illustrates the roentgenographic changes associated with the sclerosing osteogenic sarcoma. The sclerosing type of tumor may be confused with hemangioma in the sacrum but with hemangioma the sun ray effect in the periosteal zone is usually more regular and more pronounced. With osteolytic sarcoma a diffuse destructive process with irregular invasive margins is seen Osteolytic sarcoma may be confused with giant-cell tumor (Fig 586) When the sclerosing type of sarcoma extends into the soft parts, bone is produced.

High voltage roentgenotherapy was given to five of the patients with osteolytic and osteosclerosing sarcoma. Life was not prolonged, but pain was relieved. Roentgentherapy was employed in one case of chondrosarcoma of the sacrum (single primary lesion) and the patient is alive six years after onset. Radium was implanted during the treatment of one secondary chondrosarcoma (sarcoma complicating multiple exotoses) and the patient died two years after the beginning of the treatment. Roentgenotherapy is the treatment of choice for osteogenic sarcoma of the spine although it provides palliation only

Chordoma

Chordoma, which is a tumor confined to the spinal axis, has been frequently reported. In 1935 Mabrey collected 150 cases. Eighty seven of the chordomas were sacrococcygeal, 49 were cranial and the remaining 14 were distributed elsewhere along the vertebral column. Ribbert in 1894 named the tumor Most observers agree that the notochord, from which the tumor arises, is of entodermal origin. According to Mabrey's statistics, the age of greatest incidence of the sacrococcygeal tumors is from 40 to 60 years and of the spheno-occipital tumors is from 20 to 40 years. He also stated that the average duration of life for these patients is 28⅜ months, the extremes being 4 months and 18 years.

We have five cases of chordoma. In three of these the tumor was sacrococcygeal, in one occipital and in the other cervical. The ages of the patients ranged from 26 to 71 years. The patients who had a tumor in the cervical or occipital region died from encroachment of the tumor on the central nervous system. A tumor in the upper part of the cervical region may produce nasopharyngeal or pharyngeal symptoms. One of the patients with sacrococcygeal tumor had lived nine years after onset when last seen. The tumor had been excised three times and had been treated with radium. Another patient with a growth of this type was living four years after the onset. The tumor had been twice excised and in spite of roentgenotherapy was still growing and was considered inoperable. In the remaining case the tumor was twice excised, and at the second operation metastatic nodules were removed from the soft tissue of the forearm, the arm, the hip and the pectoral region. This patient was not traced after the last operation.

The roentgenogram usually shows de-

struction of bone with the shadow of a tumor in the soft tissues (Fig 592)

The tumor is slow-growing but malignant and kills by invasion of vital structures. Mabrey estimated that at least 27 per cent of the growths metastasize This is most common in the lumbosacral tumors. There were metatases from two tumors in our series, to the regional lymph nodes in one instance and to soft tissues of the thorax and extremities in the other



FIG. 592. Chordoma of the sacrum. The roentgenogram shows destruction of the body of the sacrum and a soft-part shadow The photomicrograph shows the lobulated cartilage-like structure with vacuolization of the cells.

The microscopic picture is variable. Alezials and Peyron, basing their studies on the histogenesis of the notochord in the embryo distinguished three general types. The first and most primitive type of chor

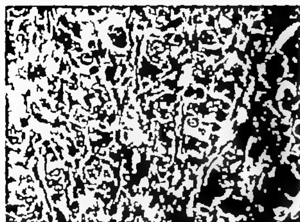


Fig 593 Photomicrograph of cellular chordoma of the epithelial type.

doma, according to their studies, should correspond to that stage in which the notochord is evaginated from the entoderm. They could, however find no tumor corresponding to this stage A second and more clearly differentiated type would be formed by solid cords of polyhedral and globular cells with abundant granular cytoplasm. Some of the cells will show vacuolation. In our series three chordomas were of this type (Fig 593) In the third stage these cells become increasingly vacuolated and a homogeneous intercellular mucinous matrix resembling hyalin cartilage is produced. Two of the tumors in our series presented a microscopic picture corresponding to that of this adult type of chordoma (Fig 592)

Irradiation seems to have little effect on chordomas. Surgical excision should be attempted, but recurrence is the rule.

SYMPATHICOBLASTOMA AND EWING'S SARCOMA

In a series of approximately 100 tumors involving the spinal cord, there were 12 which affected bone and which on microscopic examination were found to be sympathicoblastomas. These 12 tumors were types of sympathicoblastoma in all stages of differentiation

The incidence of sympathicoblastoma in this series of spinal tumors was relatively high. This type of paravertebral tumor is not generally thought to complicate the diagnosis of neoplastic lesions about the vertebral column.

The average age of onset was 33 years, the extremes of age being 15 and 66 years. Sympathicoblastoma is generally a tumor of childhood and one of the commonest malignant tumors of that period. Scott and Palmer however collected 32 cases of neuroblastoma arising from the sympathetic nervous system outside the adrenal medulla and found that the ages of the patients ranged from 1 month to 64 years. Schultz tabulated 58 cases of benign ganglioneuroma and found that 26 of the tumors occurred in adults and 22 in children. Less clearly differentiated forms of neuroblastic tumor may also occur in adults (Wright, Symmers, Barnewitz, Capaldi, Busch, Blumensaat)

In our series the incidence was equal in the two sexes. Clinically the complaints were those of pain in the back, pain at the nerve roots or symptoms of compression of the spinal cord. Four patients showed symptoms of pressure on the spinal cord. Pain in the back may precede the onset of compression of the spinal cord.

The roentgenogram showed a purely destructive osseous lesion in seven cases. In only one case was there a purely osteosclerotic lesion In three cases osteolysis and osteosclerosis were both present. In addition, a paravertebral mass was visible in four of the roentgenograms. Osteosclerotic changes may take place in the substance of the bone or may occur as a periosteal reaction.

The sympathicoblastomas in this series occurred in the thoracic or lumbar portion of the spine, with the exception of one unusual tumor which involved both the cervical and the thoracic regions. Autopsy was performed in only 50 per cent of the cases, but from correlation of the roentgenologic and the operative findings it is evident that there was a paravertebral mass extending anteriorly and laterally along the bodies of the vertebrae in 10 cases. One of the 10 tumors was a metastasis from the adrenal gland, but since it acted like a

paravertebral tumor we have included it in this series. Of the two remaining tumors, one was intradural and the other extra dural This intraspinal location is of frequent occurrence since all the neuroblastic cells must migrate peripherally from the primitive neural tube and it is possible for a tumor to develop at any point between their site of origin and their destination.

Of the 10 tumors in the paravertebral region, 8 had extended into the spinal canal through an intervertebral foramen In every instance bone was affected. These two features account for the clinical picture produced.

When seen at operation or at autopsy the tumors are friable, hemorrhagic and sometimes necrotic. Often they are not encapsulated. One tumor had a polypoid appearance. There is a definite tendency of the tumor to extend in this serpiginous fashion.

Multiple metastases to bone occurred in two instances and a single metastasis to bone in two others. The lungs were involved in four instances. Metastasis to lymph nodes occurred in one case Death without metastasis occurred in one case from fatal damage to the spinal cord. Three patients are alive without metastasis following irradiation. In the remaining two cases, follow up was not possible.

TABLE 94. CLASSIFICATION OF NEUROBLASTIC TUMORS
(From Blacklock)

I. Sympathocoblastoma (all malignant)
 (A) Undifferentiated—composed only of sympathogonia
 (B) Differentiated
  1 Composed of sympathogonia and sympathoblasts
  2 Composed of ganglion cells in addition to more primitive cells (ganglion-sympathicoblastoma)
II Ganglioneuroma (generally simple and benign)
 Composed only of mature ganglion cells

The histologic picture is variable. The growth may show neuroblasts in any stage of differentiation. An understanding of the histology must be based on histogenesis. Table 94 is a simple classification based on histogenesis which was offered by Blacklock.



FIG. 594 Photomicrograph of undifferentiated sympathicoblastoma. The tumor had invaded muscle as well as bone

The differentiation of the adult tissues of the sympathetic nervous system has been described by such observers as Bielschowsky Schultz and Scott. The neuro-epithelium of the primitive neural tube gives rise to neuroblasts and glial cells. The neuroblasts of the sympathetic nervous system form sympathogonia. These are small cells with a round or oval hyperchromatic nucleus, scanty cytoplasm and, at times, delicate fibrils. As differentiation proceeds, the nuclei become larger and more vesicular and the cytoplasm becomes more abundant. The cytoplasmic processes or the fibrils become prominent features. The cells are then sympathoblasts. As the cells approach the adult form, the nuclei are enlarged and show large nucleoli, the cytoplasm increases and acquires Nissl granules. The cells are then ganglion cells.

The pheochromocyte of chromaffin tissue also differentiates from the sympathogonia However no tumors of this type occurred in the present series.

A sympathetic neural tumor may contain any of the types of cell described in the differentiation of the neuroblast. Sym

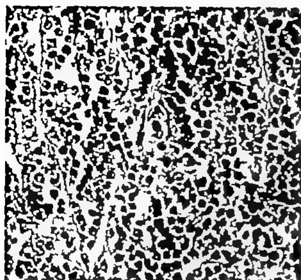


FIG. 595 Photomicrograph of differentiated sympathicoblastoma.

pathogonia and sympathoblasts are commonly present in the same tumor All three types may be present (gangliosympathicoblastoma) Sympathogonia predominate in the undifferentiated sympathicoblastoma (Fig 594) Rosettes are few and are often indicated only by clumps or balls of cells

When sympathoblasts are present in abundance fibrils are usually a prominent feature (Fig 595) Rosettes are often present. The intermingling of the two types of cells, sympathogonia and sympathoblasts, forms a microscopic picture characteristic of the differentiated sympathicoblastoma.

When the adult ganglion cell is present, the tumor is easily identified. The gangliosympathicoblastomas usually contain less-differentiated cells as well. In our case reactive bone and fibrosis were marked features.

The reaction of the sympathicoblastomas to treatment remains to be considered. Excision of the tumor followed by irradiation is apparently the treatment of choice. The relatively long duration of life in one case, in which the patient received no treatment, is explained by the fact that the tumor was of a more differentiated and less malignant form than were the other tumors.

Sympathicoblastomas are radiosensitive. One patient is well without recurrence of symptoms 17 years after the operation. Irradiation was given postoperatively Stewart and also Colville and Willis have observed that neuroblastoma (sympathicoblastoma) responds to irradiation. This radiosensitivity is a characteristic of two other neuroblastic tumors retinoblastoma (Moore) and medulloblastoma (Cutler Sosman and Vaughan) both of which resemble sympathicoblastoma in histologic appearance.

Ewing's Sarcoma

No tumors were found in this series which could unquestionably be diagnosed as Ewing's sarcoma of the spine. The remarkable similarities between this tumor and sympathicoblastoma account in some measure for this difficulty The microscopic picture of Ewing's sarcoma and that of sympathicoblastoma are strikingly similar and by the ordinary staining methods differentiation between the two is difficult. The reticulum-cell variant of Ewing's sarcoma is not unlike a sympathicoblastoma in which sympathoblasts predominate. In addition, both types of tumor may respond to high-voltage roentgenotherapy Both types of tumor also have a tendency to metastasize to one or more bones, to the lungs or to the lymph nodes.

The frequency with which multiple bone metastases are noted soon after the appearance of a primary Ewing sarcoma of bone has often been described as a characteristic of this tumor The first clinical evidence of a sympathicoblastoma may be a metastatic lesion in the skull. Coleville and Willis observed the case of an 8-year-old child who previous to death presented a typical picture of Ewing's sarcoma of the femur The age, history roentgen findings, observations at biopsy and response to irradiation were all consistent with this diagnosis. The child died five months after onset, and at autopsy a neuroblastoma of the adrenal was found, with multiple metastases to bone.

GLIAL AND SHEATH TUMORS OF THE SPINAL CORD

Glial tumors and tumors of the neural sheath and of the meninges may in some cases be difficult to distinguish preoperatively from other neoplastic lesions of the spine. It has already been shown that some of the primary or paravertebral tumors of the spine may cause neurologic symptoms as the first and only complaint. As a rule, however intramedullary tumors and benign tumors of the nerve sheaths may be diagnosed by the fact that the neurologic features are prominent and that the changes in bone, if present, are either slight or characteristic. This does not apply to malignant tumors of this type or to rare varieties of glial tumors.

Perineurial Fibroblastoma (Neurinoma)

This tumor occurs in the spine with a frequency approximately equal to that of meningeal tumors, and each is more common in this region than is glioma. Perineurial fibroblastoma (neurinoma) occurs more frequently in the lumbar and sacral region than in other parts of the spine The benign form is a firm, encapsulated, intradural or extradural tumor attached to a nerve root. It may or may not extend outside the spinal canal in hour-glass fashion. It produces symptoms of compression of the spinal cord or of the cauda equina, often associated with pain at the nerve roots (Radiculitis) Even when changes in bone occur pain in the back is not a common complaint, though localized tenderness may be present. Camp Adson and Shugrue pointed out that this tumor more commonly than any other glial or nerve-sheath tumor produces changes in the vertebral column. According to their studies, the pedicle, the laminas and the body of the vertebra are eroded in the order of frequency mentioned. The transverse process may be eroded by an extraspinal portion of the tumor Figure 596 shows erosion of the pedicles and laminas of the fifth lumbar vertebra. A lateral view in this case showed a circular defect [illegible] cm in diameter at the right intervertebral foramen. The erosion caused by these benign tumors is smooth and slight erosions are easily overlooked. Measurement of the spinal canal reveals changes in bone in a large number of the cases. Elsberg and Dyke were able by this method to detect changes in 42 per cent of 67 cases and in 70 per cent of 20 cases in which the tumors were between the tenth thoracic vertebra and the first sacral vertebra. A neurinoma may occasionally contain calcified areas which are visible in the roentgenogram, but this feature is much more characteristic of meningiomas.

In this series there were eight benign neurinomas which produced changes in bone detected in the roentgenogram or at operation No attempt was made with these or with any of the glial or nerve-sheath tumors to detect slight changes by measurement of the spinal canal

These patients are cured by simple excision.

The changes produced by sarcoma of the nerve sheath is not so characteristic in the roentgenogram as is neurinoma. There were four such tumors in this series, and in two of the cases pain in the back was a prominent complaint and preceded the symptoms of compression of the spinal cord. Destruction of bone rather than smooth erosion, was produced

Meningeal Tumors

Meningeal tumors occur more frequently in the thoracic and the cervical region than in other portions of the spine. The benign form is a firm, encapsulated, intradural or extradural tumor attached to the meninges. It may occasionally have an extraspinal portion.

There were six meningiomas in this series which were detectable in the roentgenogram by reason of gross changes in bone or calcification of the tumor Pain in the back was not a feature. Erosion of bone is less commonly produced than it is by neu-



FIG. 596 Multiple neurofibromatosis The roentgenogram shows a faint, well-circumscribed, loculated mass in the left paravertebral region Several of the pedicles of the thoracic vertebrae in this region are seen to be absent or eroded. Similar changes occur with neurinoma.

rinoma. The benign tumors cause a smooth erosion of bone. Calcification, even ossification, is not uncommonly found with these tumors and may be present in sufficient amounts to show in the roentgenogram Sarcoma of the meninges (a rare growth) causes an invasive type of destruction of bone. There was one such tumor in this series.

Multiple Neurofibromatosis

In this neoplastic condition neurofibromas may form on all the spinal nerve roots and cause erosion of bone in the region of the intervertebral foramina (Fig 596) A paravertebral mass may be visible in the roentgenogram, together with underlying destructive changes in the bone. There were two cases with this condition.

Glial Tumors

Intramedullary glioma is less common than nerve-sheath tumor in the spine and rarely produces gross changes in bone. There were but two such intramedullary gliomas in this series. One caused a smooth erosion of the laminas, and the other was demonstrable in the roentgenogram because of calcification in the tumor itself

There were six extramedullary glial tumors in this series which caused osseous changes. All these tumors may be classed as primitive, and all occurred below the level of the eleventh thoracic vertebra. There were three ependymomas and two ependymoblastomas. These tumors caused a smooth erosion of bone. The remaining tumor was a primitive neuro-epithelioma which occurred ventral to the sacrum, causing destruction of that bone.

In general it may be said that the glial tumors which cause osseous changes are of the less-differentiated, extramedullary type and that they usually occur in the lumbar and sacral regions

TERATOID AND TERATOLOGIC TUMORS

In this series there were two teratologic tumors, one an intraspinal dermoid cyst and the other an intraspinal teratoma. One occurred in the lower thoracic region and the other in the upper lumbar region. Both tumors compressed the spinal cord, and both were associated with hairy moles on the skin surface. One patient was 3 years of age, and the other 35

There were three ventral tumors in this series. One was a primitive neuro-epithelioma, which has already been described with the glial tumors. The other two were teratomas in which all three of the primitive germ layers were present. Nerve tissue elements were present in both of these tumors. Both patients were infants, one of whom died soon after delivery and the other at eight months of age.

DIFFERENTIAL DIAGNOSIS

Spinal tumor is frequently diagnosed as tuberculosis of the spine. It may be impossible to differentiate the one from the other by roentgen examination. This is true particularly in regard to the malignant tumors. Certain points deserve emphasis

Fray has pointed out that a vertebral body destroyed by malignant disease is apt to collapse uniformly producing an "accordion effect. A triangular compression of a vertebral body is more common in tuberculosis. This variation in the type of collapse accounts for the fact that a gibbus is usually less marked in a neoplastic lesion than in a tuberculous lesion. A firm type of tumor of course, may destroy a vertebral body and yet prevent any appreciable collapse. A characteristic of tuberculosis is destruction in the anterior portion of adjoining vertebral bodies, a very uncommon finding with spinal tumor Compere and Garrison stated that they have never seen tuberculosis primarily affect the neural arch or its appendages. These parts are frequent sites of neoplastic growth. Tuberculosis shows little tendency to regeneration of bone (Compere and Garrison) a marked feature with some tumors, especially after irradiation. In some cases it may be found necessary to attempt an aspiration to obtain material for culture or for microscopic examination. In general however it may be said that in the absence of compression of the spinal cord, which is a symptom requiring operative relief it is best to treat the doubtful condition by rest and by irradiation



FIG. 597 Tuberculosis of the lumbar spine. The roentgenogram shows disappearance of the intervertebral disk between the first and the second lumbar vertebrae, with sclerosis of the vertebral bodies.

Pyogenic osteomyelitis of the spine should not as a rule be confused with neoplasm The history of a preceding infection the acute febrile state and the early destruction of the intervertebral disk should establish the diagnosis. Acute osteomyelitis of the spine is uncommon compared with tuberculosis.

The lesions of the spine which also must be borne in mind are those of typhoid fever of syphilis, of fungous infection and of osteomalacia.

In any lesion of the spine in which the diagnosis is doubtful it is well to make a roentgen examination of the entire skeleton. The possibility of the presence of syphilis may be ruled out by serologic tests or by the response to specific therapy The urine should be examined for Bence Jones bodies. The response to roentgen therapy may be helpful in the diagnosis.

SUMMARY

Metastatic carcinoma in adults, usually from the breast or from the prostate is the

most common neoplastic condition of the vertebral column. Cancer of the breast may involve any region of the spine, the lesions are usually multiple and destructive. Carcinoma of the prostate involves the sacrolumbar region and produces sclerosis of bone. These multiple lesions of the spine in adults must be differentiated from multiple myeloma, which produces multiple circular defects with a tendency to pathologic fracture and collapse. Involvement of the spine in Hodgkin's disease lymphosarcoma and leukemia may simulate metastatic carcinoma.

Benign giant-cell tumor and osteochondroma are the most common benign tumors of the spine. Giant-cell tumor usually affects the spine of the young adult below the cervical region, tends to involve the neural arches and produces a trabeculated lesion outside of the body of the vertebra. The healing phase of this condition produces bone cysts, which may also complicate von Recklinghausen's disease associated with parathyroidism and demineralization of the entire spine. Osteochondromas may occur in any portion of the spine. The neural arches are affected by an osseous growth, with a clearly demarcated osseous shadow visible in the roentgenogram. Hemangioma of the vertebra is rare and produces characteristic vertical striations or well-ordered radiating spicules of bone without collapse of the body of the vertebra.

Osteogenic sarcoma of the spine, including chondrosarcoma, osteolytic sarcoma and sclerosing sarcoma, may be secondary to multiple exostoses or to Paget's disease. These sarcomas show a wide age distribution. Chondrosarcoma of the spine tends to involve several vertebrae and produces characteristic calcified paravertebral shadows. The roentgenogram in a case of sclerosing sarcoma shows irregular formation of new bone in the soft parts. Osteolytic sarcoma is less characteristic in the roentgenogram and produces a rapidly extending region of osseous destruction, with infiltration of the soft parts. Chordoma affects either the spheno-occipital or the sacrococcygeal region of the spine of the adult and produces a bone-destructive lesion, which increases gradually over a period of months or years.

Twelve undifferentiated neuroblastic tumors—sympathicoblastomas—involved the spine in the present series. Such a tumor is usually situated in the lower part of the thoracic or in the lumbar region. It destroys bone and produces a paravertebral shadow. It tends to metastasize to the regional lymph nodes and to other bones and on microscopic examination is often mistaken for Ewing's sarcoma. Like Ewing's sarcoma it responds to irradiation. No typical Ewing sarcoma of the spine was found in the present series, and the spinal tumors previously classed as such were thought on further study to be sympathicoblastomas.

A glial or nerve-sheath tumor of the spinal cord may involve the vertebral column. A meningeal tumor usually affects the thoracic or the cervical region and may be visible in the roentgenogram, either because of erosion of bone or because of calcification in the tumor. Neurinoma or neurofibroma of a spinal nerve root more often causes erosion of bone than does a meningeal tumor. Neurinoma is most common in the lumbar and the sacral regions. This benign tumor attached to a nerve root may slowly erode bone, the pedicle, the laminas and the body of the vertebrae being affected in the order mentioned. Erosion is more rapid and more pronounced with a malignant nerve-sheath tumor affecting the roots of the spinal nerves. Glial tumors producing changes in bone are rare. They are usually primitive neuro-epitheliomas or ependymomas. In the sacrococcygeal region a benign or malignant teratoma may erode bone.

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PART FIVE

Differential Diagnosis

26

Differential Diagnosis

Diseases of bone more often chronic than acute, may give rise to symptoms, to physical findings and even to features depicted by the roentgenogram which closely simulate forms of bone neoplasm The possible points of confusion are numerous. Serious mistakes can be avoided only when adequate knowledge of the various tumor processes is supplemented by a familiarity with both common and rare diseases of bone, and when, in addition, certain safeguards or rules of procedure are employed. For this reason the clinical application of the foregoing chapters may be definitely enhanced by a consideration of certain diseases of bone from the standpoint of differential diagnosis and by repeated reference to the rules of procedure contained in the introduction. From the standpoint of roentgenologic diagnosis the charts shown in Figure 599 will be found convenient for comparing the neoplastic and the nonneoplastic entities.

COMMON INFLAMMATORY LESIONS OF BONE

Osteomyelitis, tuberculosis and syphilis must be kept constantly in mind because of their common occurrence The diagnosis of all three of these conditions depends primarily upon the clinical picture rather than upon the roentgenogram

Osteomyelitis

In a child between the ages of 2 and 15 years, the occurrence of high fever (from 103 to 104°) leukocytosis (from 25 000 to 30 000) and a toxicity indicative of an acute infection plus localized pain and localized tenderness near the epiphyseal line of a long bone, without involvement of the neighboring joint, is presumptive evidence of an acute embolic osteomyelitis. Penicillin and sulfonamide therapy followed by exploration should follow in patients over 2 years and confirmation by roentgen examination which is negative at this stage of the disease should not be awaited.

The roentgenogram of an acute osteomyelitis is characteristic when bone changes have developed. At this stage there is evidence of bone destruction and new bone formation. The bone affected is typically that of a child under 10 and the area of involvement is most frequently in the upper end of the tibia, the lower end of the femur the lower ends of tibia and fibula, the upper end of the humerus, or the lower end of the radius. As Starr has stated, the area of involvement is generally triangular (Fig. 598) with the base toward the epiphysis and the necrotic areas sloping

Starr Clarence L.: Osteomyelitis, Practice of Surgery (Dean Lewis) Vol. 2, Hagerstown, Md., Prior 1929 Chap. 2.

away toward the midshaft and toward the periosteum. The periosteum is stripped for some distance by pus and gives evidence of an involucrum beneath by a dense shadow of new bone formation. Bone destruction, with the formation of sequestrum, is the rule The sequestrum is often rounded and



FIG. 598. Roentgenogram of osteomyelitis in a child aged 9 (A) shows the acute stage predominated by bone destruction (B) shows the chronic phase in the same child one year later

sharply demarcated. If the disease becomes chronic, new bone formation becomes more and more marked and irregular in character Pathologic fracture may occur

Pathogenesis of Osteomyelitis. Pyogenic osteomyelitis is divisible by etiology into two varieties the extensive and the embolic forms. *Infection* of bone by *direct extension* from neighboring tissues occurs in cases of septic amputations and compound fractures, in relation to ulceration of the soft tissues in either the oral cavity or the extremities It may arise in relation to the alveolar abscess, as a complication of dental caries. The age and causative organisms are extremely variable when infection of bone takes place by direct extension. Varieties of staphylococcus, streptococcus and anaerobic organisms may be found. Infections with *Bacillus coli* and *B aerogenes capsulatus* are not unusual. When the skull is involved secondary to chronic ulceration the gummatous infiltration of tertiary syphilis must be considered.

Osteomyelitis which occurs by extension from neighboring infected tissues is more variable in location than embolic osteomyelitis, the sites being determined by the zone of contact between the bone and the source of the infection. The sequestra usually are formed by only a part of the total thickness of the bone. With septic amputation, the sequestra come from the bone in contact with the medullary cavity and in compound fractures they form from the outer surface of the cortex.

Embolic infection of bone usually gives rise to acute hematogenous osteomyelitis with systemic reactions far more pronounced than in cases of infection by direct extension The causative organisms are

more specific. The age incidence and the anatomic localization show definite peculiarities. A primary focus such as a furuncle abscessed tooth or a generalized septicemia precedes the onset Between 75 and 90 per cent of embolic osteomyelitis is caused by *Staphylococcus aureus* Hemolytic streptococcus is next in frequency but is more often found in children under the age of two years. The *Pneumococcus* and *Staphylococcus albus* are rare offenders. The maximum age incidence of disease is in children from 5 to 14 Males are affected in a ratio of 2 1 The metaphysis of the long bones, particularly the tibia and the fibula, are the usual sites. At the sites and ages of predilection the periosteal blood supply is maximal. The process of cartilaginous resorption is in progress and opens up relatively large vascular spaces in the growing bone which are not lined by protective endothelium. Following an injury stagnant pools of blood are provided which act as an excellent culture medium for stray organisms carried about in the circulation. In adults, between the ages of 25 and 40 after ossification is complete in the long bones, acute osteomyelitis is more commonly found in the vertebra, because this spongy bone is more highly vascular in adults than the long bones.

Acute hemotogenous osteomyelitis is characterized by subperiosteal abscess formation. The tension built up in the cancellous spaces and haversian systems of the bone elevates the overlying periosteum and finds release in the subperiosteal cavity thus formed. Necrotic infarcted bone is separated from the cancellous and cortical zone by thrombosis and acute granulation tissue and may float freely in the pus cavity If the under layer of the periosteum is bathed by pus, no new bone is laid down But if the pus is evacuated, or if granulation tissue forms beneath the elevated periosteum, new bone is laid down rapidly and the periosteum thus becomes reattached to the shaft. Acute inflammation of the marrow is present in the immediate vicinity of the primary focus in cancellous bone and in rare instances the disease may extend the length of the medullary cavity and invade the opposite end of the cancellous bone In some instances, the epiphyseal cartilage may be invaded and septic arthritis may result.



FIG. 600 Roentgenogram of a case of acute osteomyelitis simulating Ewing's sarcoma.

Chronic osteomyelitis may be a residuum of acute embolic infection of bone After the evacuation of pus from the subperiosteal abscess and the onset of healing, portions of dead bone which harbor infection may persist and gradually separate themselves as sequestra The borderline between the dead and the living bone is at first marked off by suppurating or pyogenic granulation tissue With fibrosis and ossification of this granulation tissue sequestration is complete The encasing periosteal new bone which represents the healing reaction is known as the involucrum. This bone is at first porous and then sclerosed, and gradually assumes a normal texture Separation of the epiphysis may occur during the unchecked course of acute osteo-



FIG. 601 Roentgenogram showing pathologic fracture in chronic osteomyelitis.



FIG. 602. Roentgenogram of a case of osteomyelitis with sequestration arising by extension in the stump of an amputation

myelitis. It results from suppuration which extends transversely over the whole metaphyseal zone of ossification next to the epiphyseal line. If the epiphysis suppurates, septic arthritis will occur

Vertebral osteomyelitis occurs in the later age groups and usually affects young adults. Either the neural arch or the bodies may be affected. In the cervical spine retropharyngeal abscess may be a complication and in the lumbar spine psoas abscesses may occur The infection, as stated, may have its localization in the neural arch or the body of the vertebra. In the body of the vertebra, the disease is usually found just beneath the intervertebral cartilage and may extend about the intervertebral cartilage to involve the ends of two vertebral bodies on either side of the intervertebral disk. In about 50 per cent of the cases in which diagnosis is late, epidural abscess with or without meningitis may occur

The clinical distinction between osteomyelitis of the spine and tuberculosis is an important one. In pyogenic cases, the course is more rapid (two months as compared with two years) The thinning of the intervertebral disk in septic osteomyelitis is only partial, and bone destruction is accompanied by reactive new bone which produces neighboring zones of increased density in the roentgenogram. In tuberculosis there is complete collapse of the disk and rarefaction of several or more vertebral bodies.

Sarcoma when associated with acute symptoms accompanied by temperature as high as 101° F., and rarely as high as 103° F., strongly suggests a pyogenic infection Chills which may precede the fever in osteomyelitis are not a feature of sarcoma. Usually a firm tumor mass which is larger than in osteomyelitis is definitely palpable rather than the tense fluctuation of pus, but occasionally the sarcomatous mass may

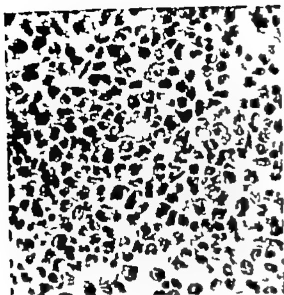


FIG. 603. (No 44899) Photomicrograph showing the leukocytic infiltration typical of osteomyelitis.

have a boggy feel. An enlargement of the regional lymph nodes may occur with malignant bone tumor but does not indicate metastases to these nodes. In our opinion, it is always a mistake to make a biopsy on the regional nodes for any type of bone lesion unless metastatic involvement of the bone itself by cancer or by a malignant melanoma is suspected.

The chief diagnostic procedure is surgical exploration of the bone itself The finding of pus at operation rules out sarcoma, whereas the finding of necrotic bone in extremely vascular tissue favors osteogenic sarcoma, which at this age is usually of the osteolytic or presclerosing type. In the absence of pus, biopsy material should be studied both microscopically for sarcoma and bacteriologically by culture for organisms (Fig 603)

BRODIE'S ABSCESS

More than one hundred years have elapsed since Brodie first described this clinical entity of bone, which is characterized by a small single focus of destruction due to a latent chronic infection in the cancellous tissue near the extremity of a long bone. Males are affected far more frequently than females (five to ten times in most of the series recorded) and the highest incidence occurs in the decade falling between the ages of 14 and 24 years. More than half of all cases reported in the literature have been located in the tibia Less frequent locations are the lower femur and lower humerus.

The duration and symptomatology reflect the etiology of the disease In a large percentage of the cases (84 per cent in Thomson's series) there is a previous history of acute osteomyelitis. Students of this condition are agreed that cases of acute osteomyelitis may develop such a Brodie's abscess as a residual or complicating feature, and that Brodie's abscess is most frequently caused by staphylococci of low virulence. Many of the patients give a history of an acute onset, the symptoms rapidly subsiding, to be followed during the period of the next months or years by variable and usually mild pains in the affected region. On examination, there is a fusiform swelling of the bone in the upper or lower tibia to aid in making the diagnosis.

In the roentgenogram the bone shows a more or less circular rarefaction in a central location in the metaphyseal region of a long bone, usually the upper or lower tibia. The cortical bone about the lesion shows increase in density and expansion, which produces a definite and palpable swelling Such a Brodie's abscess may be distinguished from a bone cyst because the involved area is considerably smaller usually from 1 to 2 centimeters in diameter there is less expansion and the neighboring cortical bone is practically always far thicker than the thin shell of bone found about the bone cyst (Figs. 604 and 605) Occasionally the area of bone destruction may be so small that it is overlooked by the roentgenologist. Pathologic fracture is extremely rare in these lesions and has not been recorded in our series.

Thomson Cited by Henderson, M S., and Simon, H. E. Brodie's abscess, Arch. Surg., 9 504 1924.



FIG 604. (No. 43646) Lateral view of a Brodie's abscess situated in the lower end of the tibia. The small size of the bone defect, the periosteal swelling, as well as the location in the tibia, are diagnostic. Nearly 90 per cent of all these lesions occur in the long bones.

Pathologically the disease takes the form of a small island of soft granular material in the medullary cavity or a small cavity filled with fluid about this there is bone of increased density The origin of the disease may be traced to a dormant focus of infection, carried to the medulla of the bone by the blood stream and remaining quiescent until the resistance of the patient is lowered by a systemic disease or locally by trauma. High fever and leukocytosis are rare, but occasionally sinus formation and a sequestrum may occur A good prognosis may be given if proper surgical evacuation of the infected area is performed.

Recently we have seen multiple abscess of the subacute Brodie type following the treatment of acute osteomyelitis by penicillin only

Clinically the lesions most frequently confused with Brodie's abscess are the benign latent bone cyst and osteoid osteoma. The latent bone cyst showing signs of reossification may simulate this form of abscess in the roentgenogram, but does not often produce the symptoms of pain and



FIG. 605 (No. 40298) Typical Brodie's abscess occurring in the femur Note the fusiform thickening of the cortical bone.



Fig. 606 Roentgenogram of sclerosing osteitis of the fibula.



Fig. 607 (No 37748) Roentgenogram of the lower tibia of a patient with Garré's osteitis. There is a diffuse ossifying lesion of the shaft with sclerosis of cortical and cancellous bone and roughening of the periosteum Note the spindle-shaped swelling produced by the widening of the shaft.

tenderness. Osteoid osteoma provokes a larger region of sclerosis than is found in Brodie's abscess. When in doubt, particularly in a lesion of the tibia giving symptoms, the area should be explored. The material obtained shows characteristic granulation tissue and positive cultures when a Brodie's abscess is present.

Garré's Nonsuppurative Osteitis

Garré's sclerosing osteitis bears a close similarity in the roentgenogram to Ewing's sarcoma. This condition runs a benign protracted course and in the typical form is rarer than Ewing's sarcoma. In German clinics it has been estimated that less than 5 per cent of all osteomyelitis is of the Garré type, a conclusion that is borne out by the statistics in this laboratory The age incidence and the site of bone involvement parallel closely the Ewing's endothelial myeloma. In our series and those reported elsewhere, practically all cases occurred before the age of 25 The lesion is solitary and frequently affects the tibia, which is involved in slightly more than half

Trendel Beitr z. klin. Chir., 12 607 1903 1904.

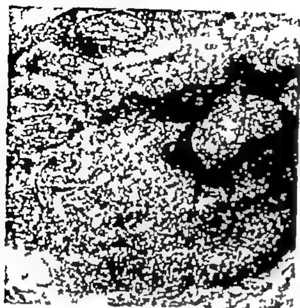


FIG. 608. (No 38784) Photomicrograph showing new bone formation in granulation tissue illustrating the typical pathologic changes seen in Garré's non suppurating osteitis.

the cases. The clinical course of Garré's osteitis, however is the reverse of that in Ewing's tumor Whereas in Ewing's sarcoma the disease begins mildly but rapidly produces acute symptoms within a few months, in sclerosing osteitis there is often an acute onset, with fever and leukocytosis, which rapidly subsides into a chronic course extending over a period of years. The pain is not severe but may be aggravated by exertion and is often worse at night. Some previous systemic infection such as pneumonia, influenza or typhoid may be recorded in the history The authors have observed several cases in young adults several years after the subsidence of a streptococcic septicemia.

In the roentgenogram the area of tumefaction may closely resemble the early stages of Ewing's sarcoma. A fusiform widening of the shaft is produced in the affected region by the stimulation of new bone formation in the periosteal and cortical zones (Fig 608) As a result of this reaction the medullary cavity is narrowed or obliterated, while the cortex is thickened and its density much increased. Ossification is more pronounced than in a Ewing's sarcoma and the "onion-peel formation" in the periosteum, typical of the Ewing's tumor is lacking.

The pathology of Garré's osteitis explains its close similarity in the roentgenogram to the early Ewing's tumor Sclerosing osteitis is the result of a low-grade infection in the haversian systems of the bone (Fig 608) which brings about an increased fibrous and fibro-osseous proliferation. Newly formed spicules of bone are embedded in chronic granulation tissue. This results in thickening of the periosteum and diminishing vascularity in the regions affected. As in the Ewing tumor the region involvement coincides in location with the osteogenic tissue, which is particularly active at this age period. New bone formation in the endosteal and periosteal layers of the bone is thus provoked.

The prognosis in Garré's osteitis is always favorable as to life, although the treatment is not uniformly satisfactory Drainage into the cortical area of the bone by multiple drill holes, or by the chiseling of a groove, stimulates vascularity and may result in cure. Healing is accelerated if penicillin therapy is added for a period of from 10 days to 2 weeks. Diathermy or the application of heat by other methods without surgical intervention and aided by antibiotics may be equally effective, but a definite percentage of the cases are refractory to treatment. On exploration these may prove to be cases of osteoid osteoma and are not of inflammatory origin. Deep roentgenotherapy should be tried first in these cases, since it constitutes a diagnostic test aiding in differentiating this lesion from Ewing's tumor Rapid shrinkage in size after the first two treatments favors a diagnosis of Ewing's sarcoma, whereas the bone changes persist in spite of irradiation in Garré's osteitis.

OSSIFYING PERIOSTITIS

This is not a separate clinical entity but a phase of bone disease seen in such dis

cases as nonsuppurative osteomyelitis of Garré, and syphilis. It is a benign condition which appears not infrequently about the tibia, humerus or femur as a single lesion surface of the bone thus distinguishing it from Garré's osteitis.

Ossifying periostitis is a chronic disease, the usual duration of symptoms averaging



FIG. 609 (No 46020) A case of ossifying periostitis in which the differentiation from periosteal sarcoma was made only after the development of the small abscessed area indicated by the arrow

in adults, generally between the ages of 15 and 35. The usual basis for this dense ossification, producing a subperiosteal swelling, is either trauma or syphilis, and in no case should a serologic test for syphilis be omitted on a patient with such a lesion The involved area is definitely circumscribed (Fig. 609) and affects usually one

nearly 18 months and in some cases extending back for from 14 to 60 years. Pain swelling and some stiffness in the neighboring joint are the usual symptoms. In 10 per cent of the cases a definite abscess carbuncle or furuncle elsewhere in the body is associated with the development of the lesion In over 10 per cent of the cases a posi

tive Wassermann test is present. One-fifth of the patients give a history of severe trauma.

Histologically the areas of ossification are caused by raising of the periosteum, following the formation of granulation tissue or hemorrhage beneath this membrane. The granulation tissue may be due to infection, following abscesses elsewhere in the body or previous systemic infection by typhoid, syphilis or influenza. The hemorrhages are most often the result of trauma. The degree of ossification produced by such subperiosteal disturbance is dependent upon the extent and character of the injury and the age of the patient In younger patients, ossification is more pronounced, and in rapidly subsiding infections and single traumas, new bone formation is likewise marked. In severe persistent infections, and in older patients, however osteoporosis is always an accompanying feature. Incision of the periosteum, with scraping of the underlying bone, is usually a successful mode of treatment in protracted cases, other than of the syphilitic type. In cases of syphilitic osteitis antiluetic therapy provides a prompt cure

The differential diagnosis roentgenologically must usually be made between the early stages of ossifying periostitis and Ewing s sarcoma. In periostitis the involvement is generally restricted to the upper layers of the cortex and the periosteum, if proper views are taken The area is uniformly dense and in the early stages there is no periosteal splitting and no secondary bone destruction. In Ewing s tumor on the other hand, there is a fine splitting of the outermost layers of the periosteum (onion peel reaction) the new bone formation extends to the inner side of the cortex and evidences of bone resorption in the medullary spaces are seen in the early stages of the disease As time elapses, the Ewing s sarcoma rapidly becomes a diffuse process in the shaft of the bone, whereas in periostitis a small abscess with sequestrum forms slowly in a localized area.

Deep roentgenotherapy aids in making the differential diagnosis. The effect on the Ewing s tumor is to cause regression, the effect on ossifying periostitis is to hasten abscess with sequestrum formation.

Tuberculosis

Tuberculosis of bone is usually a juvenile disease, caused as a rule by the bovine tubercle bacillus. Although the local focus of origin is generally in the epiphysis of the bone the symptomatology and the deformity practically always point to one of the joints the spine, hip knee and ankle being involved in the order of frequency mentioned. Chronicity and deformity are the outstanding features of this disease, the deformity being caused by either muscle spasm, shortening brought about by limitation of bone growth or actual bone destruction. In the spine, the characteristic deformity is kyphosis in the dorsal region. In the hip, a flexion deformity with shortening of the leg, is typical In the knee, flexion deformity plus the classical white swelling, accentuated by atrophy below is outstanding, while in the ankle, plantar flexion, with similar swelling, is characteristic. As in osteomyelitis and syphilis, systemic features of the disease play an important part in the diagnosis. The loss of weight, elevation of temperature in the afternoon, and systemic tuberculosis elsewhere in the body aid in making the diagnosis. In addition, the development of a cold abscess or a persistent draining sinus is typical.

Pathogenesis Tuberculosis, usually the result of infection with the bovine strain, reaches the bone via the blood stream, localizing in the cancellous tissue of the epiphysis of the long bone or a vertebra, more rarely in the periosteal region. Thus, two forms of tuberculosis of bone occur tuberculous osteomyelitis and tuberculous periostitis.

Tuberculous osteomyelitis is found usually in the epiphysis and is a progressive,

tive Wassermann test is present. One-fifth of the patients give a history of severe trauma.

Histologically the areas of ossification are caused by raising of the periosteum, following the formation of granulation tissue or hemorrhage beneath this membrane. The granulation tissue may be due to infection following abscesses elsewhere in the body or previous systemic infection by typhoid, syphilis or influenza. The hemorrhages are most often the result of trauma. The degree of ossification produced by such subperiosteal disturbance is dependent upon the extent and character of the injury and the age of the patient. In younger patients, ossification is more pronounced, and in rapidly subsiding infections and single traumas, new bone formation is likewise marked. In severe persistent infections, and in older patients, however osteoporosis is always an accompanying feature. Incision of the periosteum, with scraping of the underlying bone, is usually a successful mode of treatment in protracted cases, other than of the syphilitic type. In cases of syphilitic osteitis antiluetic therapy provides a prompt cure.

The differential diagnosis roentgenologically must usually be made between the early stages of ossifying periostitis and Ewing's sarcoma. In periostitis the involvement is generally restricted to the upper layers of the cortex and the periosteum, if proper views are taken. The area is uniformly dense and in the early stages there is no riosteal splitting and no secondary bone destruction. In Ewing's tumor on the other hand, there is a fine splitting of the outermost layers of the periosteum (onion-peel reaction) the new bone formation extends to the inner side of the cortex and evidences of bone resorption in the medullary spaces are seen in the early stages of the disease As time elapses, the Ewing's sarcoma rapidly becomes a diffuse process in the shaft of the bone, whereas in periostitis a small abscess with sequestrum forms slowly in a localized area.

Deep roentgenotherapy aids in making the differential diagnosis. The effect on the Ewing's tumor is to cause regression the effect on ossifying periostitis is to hasten abscess with sequestrum formation.

Tuberculosis

Tuberculosis of bone is usually a juvenile disease, caused as a rule by the bovine tubercle bacillus. Although the local focus of origin is generally in the epiphysis of the bone, the symptomatology and the deformity practically always point to one of the joints, the spine, hip knee and ankle being involved in the order of frequency mentioned. Chronicity and deformity are the outstanding features of this disease, the deformity being caused by either muscle spasm, shortening brought about by limitation of bone growth or actual bone destruction. In the spine, the characteristic deformity is kyphosis in the dorsal region. In the hip a flexion deformity with shortening of the leg, is typical. In the knee, flexion deformity plus the classical white swelling, accentuated by atrophy below is outstanding, while in the ankle, plantar flexion, with similar swelling, is characteristic. As in osteomyelitis and syphilis, systemic features of the disease play an important part in the diagnosis. The loss of weight, elevation of temperature in the afternoon, and systemic tuberculosis elsewhere in the body aid in making the diagnosis. In addition, the development of a cold abscess or a persistent draining sinus is typical.

Pathogenesis Tuberculosis, usually the result of infection with the bovine strain, reaches the bone via the blood stream, localizing in the cancellous tissue of the epiphysis of the long bone or a vertebra, more rarely in the periosteal region Thus, two forms of tuberculosis of bone occur tuberculous osteomyelitis and tuberculous periostitis.

Tuberculous **osteomyelitis** is found usually in the epiphysis and is a progressive

caseating inflammatory response. It gradually destroys the bone with formation of necrotic liquefying material From the cancellous focus in the end of the bone the disease may invade the joint cartilage and the joint cavity Or it may spread to the sect along the psoas muscle giving rise to abscesses when the lower vertebrae are affected Destruction of the osseous tissue of the vertebra produces collapse with angulation of the vertebral column hence the hunchback (gibbus) of Pott s disease. With



FIG. 610 (No 45124) A case of osteolytic sarcoma with clinical features of osteomyelitis. The patient was a white male aged 13 who had struck his leg 4 weeks previously and presented himself with a swelling in the region of the upper left tibia. The tumor was fluctuant, showed increased local heat, and there was a temperature of 100 8 with a leucocyte count of 10 600 At the operation blood and not pus was encountered and on the following day the leg was amputated on the basis of the microscopic section.

subperiosteal region where it produces sequestration but no involucrum because periosteal new bone is not stimulated. From the subperiosteal focus the caseating process may burrow through the soft tissues giving rise to a draining sinus or to distant subcutaneous abscesses. When the body of a vertebra is affected, the focus extends rapidly from the cancellous spaces and attacks the intervertebral disks. These are destroyed and in the roentgenogram there is a characteristic narrowing of the intervertebral spaces. The tuberculous pus may dis- gradual collapse, the spinal cord is usually not affected but it may be by sudden collapse following trauma or a major muscular effort.

Tuberculosis of the joints and tendon sheaths may be primary or secondary through extension from infection of the underlying osseous structures. Tuberculous arthritis, if primary begins as a tuberculous synovitis without involvement of the articular surfaces. In the serous or serosanguinous fluid which accumulates in the joint cavity small masses of fibrin and detached



FIG. 611 (No 27924) Roentgenogram of a tuberculous humerus showing marked destruction in the epiphyseal end of the bone with involvement of the joint.



FIG. 612. Roentgenograms of tuberculosis of the ankle joint. The bones have a characteristic "melted-ice" appearance

granulation tissue from the synovial membrane are found, which have been termed "rice bodies." Later in the process of the arthritis the articular cartilages are eroded and important periarticular structures including the joint capsule, ligaments and tendons may be destroyed. Usually there is excessive motion during the active phases of the inflammation in the joint, but with healing there may be ankylosis between the ends of the bones because of the erosion of the joint cartilages. In the region of the wrist the tendon sheaths are particularly prone to be involved. Destruction and adhesions lead to major deformities.

In tuberculous periostitis the bacilli localize in the **periosteum**. Caseating tubercles in the lower layers of this membrane destroy its bone forming capacity. As the caseating material accumulates, a subperiosteal abscess is formed which erodes the underlying bone and gives rise to cavitation. If caseation and necrosis predominate, a typical tuberculous osteomyelitis may result. If the granulation tissue is accompanied by marked fibrosis, the eroded areas are surrounded by fibrous tissue and the characteristic punched-out lesions of **caries sicca** are produced. Dry tuberculosis therefore is a form of periosteal tuberculous involvement of bone which results in both cortical destruction and the laying down of new bone.

Roentgenologic Features. In the roentgen examination of tuberculosis, there is seen a melting away of the bones which gives a diffuse haze in the region of a joint (Fig 612). The location in the spine, at the hip, knee or ankle is also characteristic. Calcified bodies about the bone in the joint or soft parts are not unusual. Subluxation occurs, while in the late stages synostosis may appear with healing, although surgical intervention is usually necessary to bring this about. Collapse of the vertebrae and actual dislocation of the hip may occur and some evidence of sinus formation may be visible in the roentgenogram.

Involvement of the neighboring joint and calcified areas in the soft parts usually typical for tuberculosis may rarely be observed in sarcoma. However involvement of both bones on either side of the joint practically never occurs in sarcoma and is an important point in differentiating malignancy from tuberculosis. A negative intradermal tuberculin test when properly carried out is against the diagnosis of tuberculosis and should never be omitted from the clinical study. Aspiration of the joint fluid

for cultures of the tubercle bacillus either by the inoculation of guinea pigs or by the use of artificial media is a helpful procedure As a last resort biopsy may be employed (Geschickter)



FIG. 613 (No 11769) Osseous syphilis. A bone-destructive process, with periosteal involvement which is characteristic of advanced syphilis.

Tuberculous Dactylitis

In infants, bone involvement with tuberculosis is often seen in the phalanges. In such tuberculous dactylitis (spina ventosa) the affected fingers or toes are enlarged and there are caseation, sequestration and sinus formation. Involvement of the phalanges accompanied by skin manifestations suggestive of tuberculosis may occur in adults (Boeck's sarcoid) In the roentgenogram the lesions of sarcoid are characterized by cystic areas of various sizes in the phalanges, metacarpal or metatarsal bones. The shafts are widened but there is no periosteal reaction Sequestration and sinus formation are rare. Microscopically the tubercles do not caseate and no bacilli can be demonstrated. The fingers and toes show characteristic deformity with swelling and shortening Ulceration and crusting occur in the skin of the hands and elsewhere. This rare form of bone involvement with hypersensitivity to tuberculosis was termed by Jüngling "ostitis tuberculosa multiplex cystica."

Geschickter C. F: Laboratory aids in surgery of the bones and joints. J Lab. & Clin. Med., 16 785, 1931.

Syphilis

Syphilis of the bone, which may be congenital but which is more often a disease of

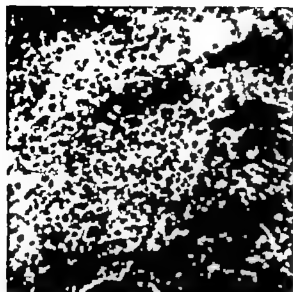


FIG. 614 Luetic osteitis The inflammatory character of the lesion under the microscope is usual for syphilis, but also similar to that seen in tuberculous involvement of the bone.



FIG. 615 (No. 4898) This illustration, together with Figures 613 and 614, depicts the bone-formative the bone-destructive and the microscopic phases of syphilis of the bone. There are sclerosis and new bone formation, with a periosteal involvement. This is an unusual picture in syphilis of an ossifying type, which is more often restricted to the periosteum.

adults between the ages of 20 and 40 is a secondary or tertiary phenomenon, although syphilitic periostitis has been described as occurring synchronously with the primary sore or from 2 to 15 weeks thereafter The history of exposure and of a primary sore plus a positive blood Wassermann reaction are essential points in the diagnosis. The osteocopic night pains are helpful in diagnosis but are not pathognomonic. Early involvement of the bone in adults is generally restricted to a periostitis, present most frequently in the cranium, ribs, sternum and the tibiae. This periostitis yields readily to antisyphilitic treatment, which restores the bone to normal. Such a therapeutic test establishes the diagnosis beyond question. In the late stages of bone involvement, gummas are usually present in the affected region, most frequently the tibia, and give a nodular character to the bone on palpation.

In the roentgenogram of syphilis which has gone beyond the stage of simple periostitis, the typical saber shin may develop if the case is a congenital one. This is marked by some bowing of the tibia, accentuated by new bone formation, incident to both periostitis and osteitis (Figs. 613 614 and 615) Gummatous osteomyelitis in adults leads to an extensive change of bone,

dependent upon both bone destruction and new bone formation, in which destruction generally predominates, producing very irregular areas, with mottling. The bone deformity resembles an ordinary chronic osteomyelitis in these cases but may be even more severe, with more mottling and irregularity. Pathologic fracture is prone to occur in gummatous osteitis.

In the final analysis there is no roentgenogram diagnostic of bone syphilis, and this systemic infection, which is prone to involve the skeleton, may mimic any type of bone tumor. The one safeguard in diagnosis is always to include the serologic reaction in the clinical study and when in doubt to give a provocative dose of arsphenamine or a therapeutic test in the form of a course of antiluetic treatment.

BONE INVOLVEMENT IN CONGENITAL SYPHILIS —SYPHILITIC OSTEOCHONDRITIS

Most children with congenital syphilis show a widening and irregularity of the epiphyseal line, the result of an interference with the normal transformation of cartilaginous tissue into bone in the growth disks. The actual presence of the spirochete and the formation of granulation tissue in this vascular and actively growing end of the long bone results in delay and incomplete conversion of the cartilaginous matrix into osseous tissue. An excessive formation of subperiosteal new bone behind the epiphyseal line is a consequence. Instead of an even and orderly transition from cartilage to calcified cartilage to ossifying tissue, there occur irregular islands of cartilage, zones of increased vascularity, osteoid tissue and islands of granulation tissue in which myriads of spirochetes can be demonstrated. When osteochondritis in the region of the epiphysis is particularly destructive, the escape of granulation tissue under the periosteum near the epiphyseal line gives rise to an exuberant fibro-osseous reaction, termed periostitis callosa.

The formation of a gummatous osteomyelitis in the medullary cavity in congenital syphilis results from extension of the disease process from the metaphyseal region. In children with congenital syphilis, who are five or six years of age, such a gumma may be found after healing of the osteochondritis has taken place. Abnormal lengthening and bowing of the bone in growing children, which gives rise to the characteristic deformity known as "saber shin," may be the result of increased vascularity to the metaphysis that accompanies osteochondritis. This has been mentioned above.

FUNGUS INFECTIONS OF BONE

The fungus infections of bone are relatively rare but collectively the osseous involvement which may occur with actinomycosis, blastomycosis, coccidioidomycosis and maduromycosis is sufficiently common to warrant their consideration in differential diagnosis. These destructive lesions of bone should be considered whenever a slowly developing osseous lesion is associated with granulomatous lesions of the lung or the skin and soft parts. The diagnosis can only be made by the demonstration of the characteristic organisms. Treatment is with massive doses of iodides. The prognosis is good if osseous involvement is the result of direct extension. With systemic involvement a fatal course is the rule.

Actinomycosis

Actinomycosis is a granulomatous infection of bone which may suppurate and form a sinus tract which discharges pus from the surface. The pus contains the sulfur granules, characteristic of this so-called "ray" fungus. Osseous involvement is usually the result of direct extension from adjacent soft tissues. Hence, the superficial bones such as the mandible, pelvis, spine and ribs are the most frequently affected. Other bones may be affected by metastatic spread via the blood stream.



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The osseous lesions are characterized by a progressive bone resorption, with little periosteal reaction The multiple areas of destruction must be differentiated from multiple myeloma, which may be simulated in the spine and ribs. At other times, collapse of the vertebrae and the formation of paravertebral abscess may simulate tuberculosis. The final diagnosis must be made by demonstrating the fungus in smear or culture. While the organism usually gains entrance through the skin or mucous membranes, when bone is involved, metastatic lesions may be secondary to pulmonary or appendiceal foci of infection.

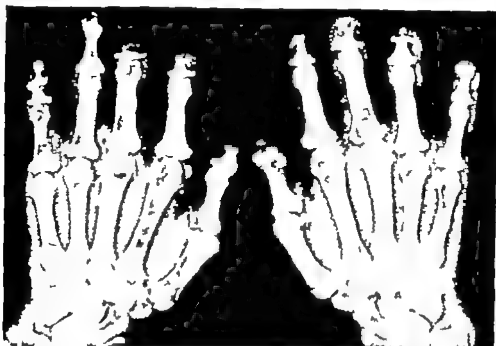


Fig. 616 Roentgenogram showing destruction of terminal phalanges in a case of leprosy

Blastomycosis

Blastomycosis is a yeastlike fungus infection, the primary focus of which is usually in the skin or lungs. Bone involvement is usually metastatic to the vertebrae, ribs and skull. Direct extension, however may occur as in actinomycosis. The lesions tend to erode bone, involve joints and produce sinus tracts (Fig. 617) The yeastlike organism can be demonstrated in the smears or in sections in the granulation tissue

Coccidioidomycosis

Granulomatous infection of bone may be the result of infection with *Coccidioides immitis* a sporulating fungus usually found in the arid regions of California, Arizona and New Mexico As in blastomycosis, infection is usually via the skin or respiratory tract. The bone-destructive lesions may be accompanied by a periosteal reaction. The bones usually affected are similar to those involved by blastomycosis. There is, however a tendency for this disease to localize in the bony tuberosities or condyles.

Madura Foot (Mycetoma)

Maduromycosis is a fungus infection of the foot, with marked swelling of the soft parts, multiple sinus tracts which ooze the characteristic granules, and secondary rarefaction and infection of the tarsal bones. A single foot is involved and the affec-



FIG. 617 Photograph and roentgenograms of blastomycosis involving the foot and elbow The osseous lesions are lytic and without evidence of new bone formation.

tion is practically painless. The appearance of an enlarged foot on a withered leg is characteristic.

LEPROSY

When involvement of the nerve trunks occurs in leprosy multiple deformities of the extremities result. The most pronounced changes are in the hands and feet, where complete destruction of the bones of the phalanges is common In advanced cases blunt stubs of soft tissue replace the fingers and toes. The progressive osseous absorption is accompanied by contractures of the joints resulting in "claw-hand" deformity Complete anesthesia of the digits leads to posttraumatic ulcerations. The mechanism of the bony destruction is unknown and is apparently not dependent on neural disturbances alone (Fig. 616)

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27

Juvenile Lesions of Bone

Osseous tumors are rare in children under five and when a neoplasm of bone does occur at such an age it is usually limited to a single bone (multiple exostoses excepted) Juvenile disturbances of the bone are usually nonneoplastic and give rise to diffuse skeletal involvement. They are either metabolic disturbances such as rickets and scurvy or congenital such as congenital syphilis, or forms of bone fragility or osteopsathyrosis. These diffuse diseases of bone are briefly outlined below more for the sake of reference than for differential diagnosis. An acquaintance with these clinical entities is important in avoiding embarrassment in diagnosis when dealing with bone lesions in extremely young patients.

SCURVY

Infantile *scurvy* is a deficiency disease due to the lack of water-soluble vitamin C. It is identical in its essentials with the scurvy found in adults, but the infantile form has a more acute onset and the character of the bony changes is influenced by the undeveloped state of the affected bones. The essential pathogenic feature is the inability of mesenchymal derivatives to form collagen-like cement substances in the absence of ascorbic acid. Thus the osteoid substances are not elaborated, and the cement substance of endothelium is lacking. The skeletal structures revert to a primitive fibroblastic pattern and the vessel lining is extraordinarily fragile and permeable. This type of scurvy begins most frequently between the sixth and tenth months of life and reaches an acute stage in two or three months In children thus affected, motion is extremely painful and there is a pseudoparalysis because of the immobile state in which the limbs are held. Hemorrhages in the neighborhood of the bone are an outstanding characteristic of the disease. The most severe of these occur beneath the periosteum and about the teeth, but they also occur in the muscle substance near the bone, or subcutaneously and hematuria is often present. The swelling about the epiphyseal line and about the joints, the extreme pain on pressure in these regions, subcutaneous hemorrhages, and the purple bleeding gums form a typical clinical picture.

In the roentgenogram (Fig 618) there is, behind the epiphyseal line, a marked increase in the density of calcification, described as "the white line," and the small epiphysis may have a characteristic *ring* about its edge. Behind the dense line areas of rarefaction are frequently seen, and at these sites epiphyseal separations may take place Subperiosteal hemorrhages followed

by a slight amount of new bone formation are seen in advanced cases but may be slight and easily overlooked in an early stage. Usually it is difficult to detect the subperiosteal hemorrhages until healing begins, when the hemorrhage during the healing process calcifies. The disease, even



Fig 618 (No 72863) Roentgenogram of a case of scurvy showing the dense line just behind the epiphysis and the periosteal involvement, in the femur typical of this disease (Dr E. A. Park)

when advanced, ordinarily yields promptly to the administration of orange juice or other antiscorbutic substances.

RICKETS

Rickets is a nutritional disturbance affecting the calcium and phosphorus balance and leading to marked bony changes. It is found in children suffering from a deficiency in fat-soluble vitamin D. Absence or insufficient amounts of vitamin D causes



Fig 619 Photomicrograph showing subperiosteal hemorrhage in scurvy

defective absorption of calcium from the gastro-intestinal tract. While there are a few scattered cases of late rickets in patients between the ages of 12 and 20 the usual age of onset varies between 4 months and 2 years. The leading deformities are in the skeleton.

These skeletal changes lead to a variety of deformities and symptoms including enlargement of the epiphyseal junctions (beaded ribs) softening and bending of bones stunting of growth, the formation of osteoid rather than osseous tissue in the metaphysis of the bones right-angle new bone in severe rickets along vessels in the subperiosteal osteoid tissue· delay in ossification of cranial bones, with persistence of sutures and fontanelles irregularity widening and saucerization of the epiphyseal lines on roentgen examination generalized weakness and irritability muscular hypotonia and excessive sweating and delay in eruption of teeth, with defects in their calcification.

An adequate intake of vitamin D permits absorption of calcium and phosphorus from the intestinal tract. With vitamin D defi-



FIG. 620 Roentgenogram of a case of rickets showing the saucer like changes at the epiphyseal line

ciency the lowered calcium absorption stimulates hyperfunction of the parathyroid glands, which restore the blood calcium at the expense of the osseous matrix. The matrix yields calcium because the serum phosphorus is lowered through increased excretion a result of parathyroid hyperplasia.

In normal children the serum calcium level is 10.2–11 0 mg per cent and the serum phosphate level is from 4.5 to 6.8 mg. per cent. The excretion of phosphorus lowers its blood level from 3–0 6 mg per cent. Rickets does not occur until the calcium level begins to fall below 9 or 8 mg per cent. The minimum normal product is $Ca \times P = 30$ Rickets occurs when the product falls below 30

The withdrawal of calcium from ossified skeletal tissue during active ossification removes the normal end point of ossification and leads to the proliferation of osteoblasts. This causes a rise in the blood alkaline phosphatase

During normal ossification, the resorption of old bone and the building up of new spicules proceed side by side. In rickets, as spicules of bone are resorbed, they are replaced by osteoid tissue which fails to calcify In growing bones the normal histologic zones behind the epiphyseal line have the following characteristics The zone of proliferating cartilage is next to the epiphyseal line. The cartilaginous cells are arranged in rows the cells farthest from the epiphyseal line are enlarged and undergo calcification The zone of provisional calcification is formed by these calcified cartilaginous cells. Blood vessels invade and resorb portions of the calcified cartilage this is the zone of vascular areolar spaces. Osteoblasts are applied to the vascularized areolar spaces and osseous spicules are formed. This is the zone of ossification These zones appear in orderly sequence.

The abnormalities observed in rickets are as follows The zone of cartilaginous proliferation is widened two to five times normal size, and the alignment of cartilage cells is disturbed. The zone of provisional calcification is present only in patches or disappears. The vascular areolar spaces are filled by proliferating fibrous tissue sprinkled with lymphocytes. Vascular spaces invade osteoid tissue in desultory irregular fashion. The zone of ossification is replaced by osteoid tissue, without calcification. Periosteal new bone, with right-angle spicules, may be formed about the metaphysis.

Administration of vitamin D decreases phosphatase and the excretion of phosphates, because the parathyroid activity subsides and there is no mobilization of calcium from the bones.

In the roentgenogram the most important diagnostic feature is a "saucer shaped" epiphyseal line, which is widened and extremely irregular as a result of the failure of normal calcification, and the accumulation of large amounts of osteoid tissue in the place of normal bone. Periosteal changes may also occur with a resultant widening of the shaft, as nature attempts to compensate for the weakness of the bone as a whole. Softening of the bones may be

marked throughout, and if the child has walked, bowing of the tibiae may be extreme. There are also characteristic deformities of the legs that result from the postures assumed when the child sits, even though he has never walked. The sternal ends of the ribs show widening or fracture The spine shows a single long posterior curve from the cervical region downward, with a compensating anterior curve in the neck. The pelvis is deformed either by flattening in the anteroposterior diameter or by funnelling due to the pressure of the femurs upward. The skull has a square appearance, flat on top and long in its anteroposterior diameter with a tendency to bossing in the parietal and frontal regions.

BONE DISTURBANCES ASSOCIATED WITH COMPENSATORY PARATHYROID HYPERPLASIA (EXCLUDING INFANTILE RICKETS—VITAMIN D DEFICIENCY)

In an earlier chapter (Chap 14) bony demineralization with bending deformity and cyst formation resulting from parathyroid adenoma were described as a form of osteitis fibrosa or von Recklinghausen's disease. Diffuse hyperplasia of the parathyroid gland occurs when either calcium or phosphorus metabolism is markedly deranged. This hyperplasia is found in juvenile rickets, described above. It is also observed in chronic glomerulonephritis, where there is retention of phosphates, and in congenital anomalies of the urinary tract with chronic uremia, acidosis and hyperphosphatemia. In this condition in order to keep the product of calcium and phosphate ions constant, there is an increased excretion of calcium, and in turn a mobilization of calcium from the bone. In these cases, the parathyroids are diffusely enlarged. The hyperplastic glands show a proliferation of the water-clear cells, and all the parathyroids are affected. The blood-phosphorus levels are usually increased, and the calcium levels suppressed. Calc. in the urine is elevated. The bones show rarefaction near the epiphyseal lines, which fail to fuse. Pathologic fractures may occur Subperiosteal erosion of the bone at the metaphysis may occur together with slipping of an epiphysis. Roentgenograms of the skull may show the "woolly" appearance found in Paget's disease. Cyst formation is usually not present, and giant-cell tumor formation has never been observed, although it is occasionally seen in primary hyperparathyroidism. If the condition occurs in children, dwarfism, or at times true infantilism, occurs. The condition is known as renal rickets or renal osteodystrophy

SUBVARIETIES OF RENAL OSTEODYSTROPHIES

Because juvenile rickets has been largely controlled in this country the renal osteodystrophies are receiving increased attention. Among the numerous subvarieties described, four are worthy of mention.

Related to Increased Bone Destruction

1. **Renal Osteitis Fibrosa Cystica Generalisata ("renal rickets")** This results from renal disease involving both tubules and glomeruli. Retention of acid metabolites and inability of the kidneys to conserve base lead to increased excretion of calcium in the urine. Lowering of serum calcium results in parathyroid hyperplasia and consequent fibrotic and osteolytic bone lesions. Because of phosphate retention, calcium complexes are normally deposited in newly formed osteoid tissue.

2. **Primary Hyperparathyroidism With Renal Changes.** The marked increase in urinary calcium excretion may give rise to secondary renal disease. By means of the mechanisms noted above, parathyroid hyperpl[illegible] superimposed on the existing p[illegible] *and the bony* lesions [illegible] much more marked severity

RELATED TO RENAL ACIDOSIS WITH DECREASED BONE FORMATION ("RENAL OSTEOMALACIA")

3. **"Tubular Insufficiency Without Glomerular Insufficiency"** (Albright) In this condition there is inability of the tubules to secrete an acid urine or form ammonia, with consequent loss of calcium in the urine due to its substitution as a base. Lowering of serum calcium leads to parathyroid hyperplasia, and as the glomeruli are not affected, increased excretion of phosphates occurs in the urine. Because of consequent lowering of serum phosphorus, calcium is not deposited in newly formed osteoid tissue.

4. **Fanconi Syndrome** This condition seems to result from an abnormal excess of acid metabolites presented to the kidney for excretion. The normal compensatory mechanisms are overwhelmed, calcium is drawn from the serum to aid in the excretion of such metabolites and further changes occur as noted under Type 1 The defect may be in the tubules and of such a nature as to inhibit normal reabsorption of amino acids although it is possible that there may be abnormal metabolism of amino acids elsewhere in the body Disorders of cysteine metabolism associated with bony lesions may fit into this syndrome.



FIG. 621 Roentgenogram in congenital syphilis showing irregularity of the epiphyseal line and marked periostitis.

In **celiac disease** or steatorrhea, the deficiency of pancreatic juice leads to faulty fat digestion in the intestinal tract. The calcium salts are precipitated as insoluble calcium soaps, in the intestinal tract, resulting in poor absorption of the calcium. In this condition, as in infantile rickets, the calcium-serum level may drop markedly and also the serum phosphorus. Tetany may occur when the serum-calcium level falls below 6 mg. per cent the phosphorus level may fall below 2.5 mg per cent. The excessive fecal excretion of calcium lowers the urinary calcium excretion to almost zero.

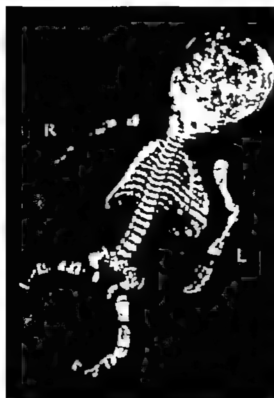


Fig 622 Roentgenogram of the complete skeleton of a stillborn child with osteogenesis imperfecta. (From Knaggs Diseases of Bone, Wood, Baltimore, 1926 p 376)

ith vitamin A and vitamin D absorption s decreased, because they are fat-soluble. In this condition, known as pancreatic ckets, the demineralization of bone is simr to that observed in renal rickets, deribed above

CONGENITAL SYPHILIS OF THE BONES

This is discussed in the preceding chap: on inflammatory diseases. Only the dif rential diagnosis is considered here. Congenital osseous lesions due to syphilis ay be manifest early in the second or ird month of infantile life or may remain tent until adulthood. In the infantile m, an epiphysitis or osteochondritis of e long bones is the common lesion. Be nd the epiphyseal line, which has a wid ed and moth-eaten appearance, the shaft widened by subperiosteal callus formation (Fig 621) In the roentgenogram, the lesion must be differentiated from rickets and scurvy Rickets is ruled out by the appearance of the epiphyseal line and by the more diffuse rarefaction of the shaft in con trast to the patchy moth-eaten rarefaction of syphilis. Scurvy may also show the type of periosteal involvement seen in congen ital syphilis but the appearance of the bone as a whole and the type of epiphyseal change is different.

The diagnosis rests not only upon the bony changes but upon the clinical picture. Snuffles is usually present, and skin lesions typical of congenital syphilis, may also be found. In addition the Wassermann reac tion is usually positive. Hutchinson s triad —the notched, peg-shaped central incisors of the second dentition, interstitial keratitis and deafness due to labyrinthine disease—is not seen until later childhood, long past the age period at which the typical osteochon dritis above described occurs.

Later in infancy (second to third year) syphilitic dactylitis is common and shows a spindle-shaped swelling, complicated by bone destruction and new bone formation occurring most frequently in the fingers, more rarely in the toes. A gummatous osteitis may also occur in the long bones, caus ing bone destruction, usually circular in outline, overlaid by a diffuse periosteal reaction.

The bossing of the skull by periosteal new bone and craniotabes marked by osseous rarefaction, described in congenital syphilis is more typical of rickets and when found in syphilitic children is probably due to this complication.

Latent congenital syphilis may affect the osseous system and appears usually in the decade between 15 and 25. The most char acteristic change is a periostitis and an anterior bowing of the tibiae, the so-called saber-shin. Diffuse osteitis with the irregu larities of the cortex and large areas of bone destruction, however may occur and we have observed two such cases of latent congenital syphilis in adults past the age of

20. In this latent adult form the disease must be differentiated from metastatic carcinoma of bone and multiple myeloma These two malignant neoplasms usually appear after the age of 35 rather than in the



FIG. 623 (No. 25247) Roentgenogram illustrating fracture deformities in a case of fragilitas ossium showing very well the bloated and expanded ends of the bone which are unusually broad and foamy in appearance. The fracture in the splinted leg has occurred through a cystic area

teens and twenties," and the Wassermann reaction, which should never be omitted in the clinical examination, aids in making the distinction.

BONE FRAGILITY

Idiopathic bone fragility has been described in numerous forms and under a group of conflicting terms. Among the German authors many of these lesions have been grouped together under the name of idiopathic osteopsathyrosis comprising several well recognized varieties, including

(1) Osteogenesis imperfecta, a nonhereditary disease, with multiple fractures present at birth the infants usually die.
(2) Fragilitas ossium, an hereditary form, accompanied by such features as brittle bones, blue sclerae, deafness and loose joints, also a proneness to pathologic fracture.
(3) Marble bones, or Albers-Schönberg disease, which is characterized by dense lime rings in the metaphyseal

and epiphyseal regions of the long bones, pathologic fracture and excessive calcification in periarticular structures.

Information at the present time is not sufficient to permit of a rigid separation of these various forms of bone fragility although in well-defined cases it is often easy to classify the condition under one of the three heads given above. More often the exact nature of the osseous change is obscure and does not lend itself to classification In the brief descriptions given below typical forms have been chosen



FIG. 624. (No. 25247) Shows a pronounced coxa vara, with multiple fractures about the necks of both femurs. Same case as shown in Figure 623

Osteogenesis Imperfecta

In outspoken cases of osteogenesis imperfecta, the children are either stillborn or survive only a short time This is known as the congenital form. The skeleton is riddled by spontaneous fractures of the extremities and ribs, with consequent deformity and shortening The ossification in the skull is usually very incomplete. Typical cases have been cited by Knaggs* (Fig. 622) The cortical bone is thin and cancellous in structure. The marrow is largely replaced by fat and a delicate fibrous tissue. In cases that survive infancy and reach childhood (varying in age between 8 and 12 years) marked bending of the bones may occur with development of cystic areas. In some cases the first indication of the disease is the occurrence of pathologic fractures when the child learns to walk. The numerous fractures may heal but the deformity continues and nonunion at one or more sites is the rule.

Fragilitas Ossium

Fragilitas ossium, which is also referred to as osteogenesis imperfecta tarda, is more frequent between the ages of eight and sixteen, and is probably best represented by the well-defined group referred to as "brittle bones" and "blue sclerae." This

*Knaggs, Robert Lawford. The Inflammatory and Toxic Diseases of Bone: A Text-book for Senior Students, Baltimore, Wood, 1926.



FIG. 625 Roentgenogram illustrating osteosclerosis, or marble bones. Typical sclerosis of the metaphyseal and epiphyseal regions, affecting a child who had multiple fractures. (Dr George G Davis.)



FIG. 626 (No 42605) Roentgenogram showing bone dystrophy in a white male, aged 7 in which there is new bone formation restricted to the diaphyseal regions. The new bone formation also involves the skull, occluding various foramina. This is an unclassified juvenile bone dystrophy closely allied to marble bones.

disease is practically always of the hereditary type, being transmitted from parents to children in a direct fashion The outstanding clinical characteristics are the fragility of the bones, with accompanying fractures and deformities, the blue color of the sclerae, and deafness, which is generally of the otosclerotic type. Optic atrophy is not usually present, which helps to distinguish this group from "marble bones" in which gradual occlusion of the foramina in the skull occurs.

In the roentgenograms the bones have a characteristically thin cortex, except where repeated fractures have stimulated increased ossification. The shafts of the long bones are more slender than normal, whereas the ends, including the metaphyses and epiphyses, are unusually broad and foamy in appearance. Slight bowing is present in most of the long bones, which may be markedly increased by fractures and malunion. Key* reports 70 per cent of fractures in the cases reviewed by him (Figs. 623 and 624)

Osteopetrosis or Marble Bones

This appears to be the rarest form and the most recently recognized of the group of cases in the bone-fragility class. It is essentially a disease of children although Reiche described a case in a man aged 37 The usual age is between 12 and 20 years. The disease is characterized by an in

* Key J Albert: Brittle bones and blue sclera: hereditary hypoplasia of the mesenchyme, Arch. Surg., 13 523, 1926.

creased thickness and density of the cortical and spongy bone and affects the entire skeleton The marrow cavity is narrowed or obliterated and in the roentgenogram the bones appear opaque, lacking their finer trabeculated structure. The patients may suffer from leukopenia, pathologic fracture, osteomyelitis and hydrocephalus. The leu kopenia may be accompanied by enlargement of the liver spleen and lymph nodes. Several members of one family are often affected and the disease may be hereditary In a survey of 121 cases, Drukker found a familial incidence in 40 per cent.

Primitive cells of both the erythroid and myeloid series may be found in the periph eral blood. In certain cases the hematologic abnormalities completely dominate the clinical picture.

Metabolic studies by Kramer Yuska and Steiner have shown normal levels in the blood for calcium magnesium, phosphorus and phosphatase. Chemical examination of the bone showed hypermineralization and an increase in the carbonate content. The underlying defect appears to be an inability to resorb bone, so that when new bone is laid down during growth, the old bone is not removed. This may lead to pinching of nerves at their points of exit from the skull Van Creveld and Heybroek report blindness due to optic atrophy as an initial symptom.

Clinically these patients come under observation because of pathologic fracture or abnormalities in the cranium. The sella turcica may be small and narrowing of the cranial foramina, with consequent optic atrophy may occur The teeth are usually decayed and poorly formed. Calcification about the ligaments has been described, with occasional premature calcification of the vessels. The roentgenogram of the bones is characteristic. The metaphyses and epiphyses of the long bones are sclerosed by increased calcification (Fig. 625) while the small bones of the hands and feet and the vertebrae show a definitely increased compactness originating in similar zones. Pathologic fractures are frequent. Characteristic transverse rings of calcification at the ends of the long bones have been referred to in the literature as a diagnostic feature. The children affected are generally poorly nourished, and are apt to die of intercurrent infections.



Fig 627 Roentgenograms of marble bones in an adult.

CHONDRODYSTROPHIA FOETALIS

The chondrodystrophics are dwarfs with a large head and a saddle nose produced

by dissociation in the development of the membranous and cartilaginous bones, the former developing normally and the latter failing to undergo their usual ossification (Fig 628) The shafts of the long bones are short, with dense cortex, poorly developed medullary cavity and rather large epiphyses. The head of the femur is small there is coxa vara of the neck and a rotary deformity of the shaft. Deformity of the fingers is usually present The bodies of the vertebrae are wedged shaped with widened cartilages between them. There is generally a marked lordosis. The pelvic outlet is narrowed. Roentgen examination discloses delayed ossification and fusion of the epiphyses. The epiphyseal cartilaginous plates are uneven and tend to flare. Coxa vara and disturbances in the head of the femur aid in diagnosis. In the skull a premature synostosis is noted.

The pathologic findings are characteristic. The cartilage of the epiphysis is penetrated by an abnormal number of blood vessels. The epiphyseal line is distorted and irregular The metaphysis near the epiphyseal line shows marked reduction in activity and bone production is decreased and irregular The medullary cavity is reduced by *endosteal* bone formation and small marrow spaces filled with marrow are few in number

The disease is congenital and usually hereditary No effective therapy is known but these dwarfs have well-developed musculature and lead apparently normal lives.



Fig. 628 (No 45950) Chondrodystrophia foetalis in a stillborn infant. Note the large head, saddle nose and deformity of the fingers.

EXCESSIVE CALLUS OF THE NEWBORN

In infants shortly after birth, tenderness and swelling of an extremity may be observed and roentgen examination may show a marked degree of periosteal new bone, extending along one or both margins of a long bone. The author has observed this in several cases in the femur of newborn infants, as well as over the scapula. Occasionally a line of fracture may be observed in the bone beneath the callus formation Often no such fracture line is visible This overgrowth of periosteal bone in response to birth injury may be regarded as an ossifying hematoma or excessive callus formation. In the early cases, it was confused with osteogenic sarcoma. The important clinical features are the extension of the periosteal new bone over the entire half or two-thirds of a single bone a well-defined outer margin of new bone formation and the tendency of the growth to appear shortly after birth, and to subside in from 6 to 12 weeks.

ASEPTIC NECROSIS OF BONE

Moore believes that the aseptic necrosis of an epiphysis of unknown etiology is the

underlying pathologic process in a group of diseases of various bones designated by the names Osgood-Schlatter's disease of the tibial tubercle, Köhler's disease of the tarsal scaphoid and patella Kienböck's disease of the carpal semilunar and Legg Calvé-Perthes disease of the proximal epiphysis of the femur



FIG. 629 (No. 36566) Roentgenogram of excessive callus formation of the newborn. The baby was 16 days old when the film was made.

OSGOOD-SCHLATTER'S DISEASE

This disease is often known as traumatic separation of the tibial tuberosity It occurs in youth before the tubercle has become firmly attached to the shaft and results from violent muscular strain exerted through the quadriceps tendon The tibial tubercle is an extension of the upper epiphyseal cartilage and does not unite with the shaft until the end of the adolescent period. The lesion may occur at any time from the age of twelve to seventeen years. The lesion is characterized by local pain and tenderness. Diagnosis is made by roentgenograms in which a comparison is made between the affected and the unaffected sides. Strapping which prevents transmission of muscular pull through the quadriceps tendon suffices to cure it.

KIENBÖCK'S DISEASE

Kienböck's disease is a postraumatic osteoporosis of the semilunar bone of the wrist which follows an interference with its blood supply In the roentgenogram a central area of rarefaction is surrounded by a ring of condensed bone. A similar



FIG. 630 Legge-Perthes disease—degenerative phase.



FIG. 631. Legge-Perthes disease—regenerative phase.

condition was described in the carpal navicular bone by Prieser

PERTHES DISEASE (OSTEOCHONDRITIS DEFORMANS COXAE JUVENILIS)

Perthes disease is a lesion of the head and neck of the femur occurring in children usually between the ages of four and nine years. It is about three times as common in boys as in girls. The child limps and there may be some pain, but rarely fever or leucocytosis. The disease is bilateral in about 10 per cent of the cases. Trauma is believed by many to play an important role, but this is not an adequate explanation of the bilateral form. The structure of the diseased bone suggests an aseptic necrosis and may be the result of a local metabolic deficiency

The earliest changes noted in the roentgenogram are increased density of the epiphysis with flattening, moderate rarefaction of the metaphysis and increased depth and sharpness of the joint cavity In later stages, the epiphysis becomes more flattened and fragmented, the neck of the femur becomes broader and there is maladjustment of the femur to the acetabulum There is a degenerative phase which lasts one year or more, followed by a regenerative phase of similar duration. The best results are obtained by preventing weight on the diseased joint until the regenerative phase is complete. Upon exploration, the articular cartilage is found to be smooth, although it is often deeply grooved. The cartilage is normal, microscopically but there is necrosis and disintegration of bone in the epiphysis under the articular cartilage.

KÖHLER'S DISEASE

Köhler s disease affects the tarsal navicular (scaphoid) bone. This lesion develops in children, usually between the ages of three and seven years. There is pain in the foot after exercise. The foot may be swollen and the region of the navicular bone is sensitive to pressure. On roentgenographic study the navicular is compressed anteroposteriorly and the structure is denser than normal. The anomaly is often bilateral, and sometimes without symptoms in one foot and painful in the other

OSTEOCHONDRITIS DISSECANS

This disease occurs during adolescence and is more common in males. It usually affects the knee joint, less often the elbow

and rarely other joints. The patient may seek medical assistance because of locking of the knee, or he may complain of a troublesome knee that gives way or locks at times. The knee may be swollen and painful. Occasionaly there are no symptoms, the disease being discovered accidentally Some cases are bilateral Roentgenographic study reveals an eroded area of cartilage nearly always on the internal condyle of the femur and usually one or two loose bodies in the joint cavity The loose bodies are responsible for the locking of the joint. Exploration of the joint reveals an ulcerated area of cartilage extending into the bone. The loose bodies arise from this area and are composed of cartilage and bone.

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28

Endocrinopathies and Rare Diseases of Bone

Most metabolic diseases and growth disturbances of bone are clinically manifested in childhood and the more common diseases in this category have been discussed in the preceding chapter In the present chapter endocrine disturbances and a group of rare diseases of bone of unknown etiology are considered. A group of toxic manifestations in bone are also included.

OSSEOUS CHANGES WITH ENDOCRINE DISTURBANCES

Normal bone growth prior to adulthood is unquestionably under the control of the pituitary gland. The ossification behind the epiphyseal line, the appearance of centers of ossification in the epiphysis, and the laying down of cortical and cancellous bone in the triangle made by the junction of the epiphysis with the cortex are all interfered with in the presence of marked endocrine disease The extent of bone development, expressed in terms of bone length and bone density together with the time of union of the epiphysis, are major indices of endocrine activity to which may be added the time and quality of dentition The closure of the fontanelles has a similar significance The activity of the gonads stand in reciprocal relationship with the activity of the pituitary *With hypergonadism there is retarded growth similar to hypopituitarism. With hypogonadism there is accelerated growth, similar to hyperpituitarism* Hyperparathyroidism and hyperthyroidism, are similar in effect to hyperpituitarism, with which they are probably associated. Hypothyroidism, on the other hand, is similar in its effects to hypopituitarism, with which it is associated. Cushing's syndrome which may be associated with basophilic adenoma of the pituitary or of the adrenal cortex after childhood is an exception. These features are brought out in the accompanying tables (Tables 95 and 96)

Hyperpituitarism (Giantism and Acromegaly)

This condition is the result of eosinophilic adenoma of the anterior hypophysis. In giantism, the bones present no individual peculiarity There is unusual lengthening of the long bones prior to the union of the epiphyses, and the cortex may be thicker When the pituitary disturbance persists into adult life or when it occurs in the later

age group there are characteristic skeletal changes. In acromegaly there is overgrowth of the hands, feet and face and enlargement of the tongue, nose and lips. The terminal phalanges are broadened. The cancellous spaces in the bones are enlarged and there is deposition of periosteal new bone. In the skull, the sella turcica, frontal and other paranasal sinuses are enlarged and there is erosion of the posterior clinoid process. Cystic areas may be formed in the condyles or trochanters of the long bones. The thickness and size of the mandible is increased and there is enlargement of the anteroposterior diameter of the vertebrae. Atkinson found a kyphosis (usually lower dorsal) in 351 of 584 patients with acromegaly Some of the characteristic features are the increased angle of the mandible, with prognathism, and separation of the teeth. The occipital protuberances are more prominent. The supra-orbital ridges are enlarged. If treated early this form of hyperpituitarism may be controlled by irradiating the hypophysis.

TABLE 95 SKELETAL AFFECTS IN ENDOCRINOPATHIES

HYPERENDOCRINISM The common factor is probably pituitary overactivity There is a tendency to increased bone length, osteoporosis, enlarged cancellous spaces, and cyst formations. The gonads are the exception, and stand in reciprocal relationship to the pituitary The above affects, therefore, are seen with hypogonadism

Hyperpituitarism

- Basophilism Osteoporosis compression fractures of the spine.
- Eosinophilism Acromegaly in adults. Periosteal deposition of new bone kyphosis, with increased diameter of the vertebrae enlargement of the cancellous spaces, with cyst formation in the condyles.
  Giantism in children. Increased length of long bones more rapid epiphyseal growth.

Hyperparathyroidism. Osteoporosis increased calcium mobilization multiple cyst formation bending deformity

Hyperthyroidism. Diffuse osteoporosis, with occasional cyst formation in the femur compression fractures in the spine increased calcium mobilization.

Hyperplasia of the Adrenal Cortex: Similar to basophilism Osteoporosis and compression fractures of the spine.

Hypogonadism (Reciprocal effect stimulating pituitary overactivity)

- Fröhlich s Syndrome Tendency toward giantism.
- Prepubertal Hypogonadism Retarded epiphyseal closure increased bone length subcalcification thinning of cortex and bony trabeculae.
- Menopausal Syndrome Generalized decalcification, maximum in spine tendency to compression fractures.

TABLE 96

HYPO-ENDOCRINISM The common factor is probably pituitary underactivity Bone density is increased, particularly behind the epiphyseal line Bone length is shortened. The ossification centers in the epiphysis are delayed. The gonads are the exception and stand in reciprocal relation to the pituitary Bone length is therefore shortened by hypergonadism.

Hypopituitarism. If this occurs at birth, there is dwarfism. In general, there is retarded bone growth the reverse of hyperpituitarism. There is a tendency to increased ossification behind the epiphyses, giving lines of density

Hypothyroidism

- Cretinism Delayed centers of ossification at the epiphysis increased density at the metaphyseal line retarded lengthening of bones.
- Juvenile Myxedema Delayed dentition and closure of fontanelles. Increased bone density, due to calcium retention epiphysitis, resembling Legge-Perthe's disease.
- Adult Myxedema Increased bone density due to calcium retention.

Hypergonadism. Premature closure of the epiphysis. Bones are shortened, but otherwise normal.

BASOPHILIC ADENOMA OF THE PITUITARY (Cushing s Disease)

Basophilic adenoma of the pituitary is accompanied by obesity hypertension and suppression of sex function in men and women. The osseous changes are characterized by demineralization, with a resulting kyphosis and compression fractures of the vertebral bodies. It is rare to find any alteration in the size of the sella turcica. The pathologic condition of bone associated with Cushing s disease has many of

Fig. 632. Roentgenogram of pituitary giantism in a boy ▮ feet, 10 inches in height, aged 18 years. The epiphyseal line of the upper humerus is not closed.

the clinical characteristics of postmenopausal osteoporosis. In this disease there is a decrease or an absence of the formation of estrogen and, in addition, an increase of urinary androgens. Gardner and Pfeiffer have found that testosterone inhibits the effect of estrogen on the formation of bone in doves, and it is possible that an excessive increase in androgens which is found in Cushing's disease may accentuate the osteoporotic changes. Albright feels, however that the important factor in the causation of osteoporosis in this syndrome is the negative nitrogen balance due to an increased conversion of proteins into sugars. For this reason, he feels that testosterone therapy as an anabolic stimulator is effective in treating Cushing's syndrome.

HYPERFUNCTIONING ADRENAL CORTEX

The adrenogenital syndrome in children is characterized by hyperplasia or tumor formation of the adrenal cortex. The syndrome is also called pubertas praecox. In girls there is masculinization and hirsutism, with growth of the clitoris. In boys, there is premature sexual development and a Herculean build. In these patients, there may be a transient overgrowth of bone with incipient giantism, followed by premature closure of the epiphyses. The accelerated bone age accompanies the precocious puberty or virilism in girls, and is characteristic of overactivity of the adrenal cortex. The 17 ketosteroid content of the urine is increased. In children approaching puberty tumors of the adrenal cortex produce the characteristic Cushing syndrome de-

Fig. 633. Roentgenograms of skull in acromegaly (*Left*) The anteroposterior view shows the enlarged frontal sinuses and the enlarged, broadened mandible. (*Right*) The lateral view shows an enlarged sella turcica.

scribed above. In girls, there is flattening of the breasts and amenorrhea, and in girls and boys there is girdle obesity purple striae, a tendency to acne plethoric countenance, polycythemia, and "pig eyes." In the skeleton, there is osteoporosis of the skull and spine The lower ribs, near the costochondral junctions, may be twice their normal diameter a rather unique feature of this condition

Hypopituitarism

If there is marked insufficiency in the growth factor pituitary dwarfism occurs. The bones are relatively normal except for their size. The epiphyseal union is delayed and may never take place. The skull sutures remain open. This severe form is accompanied by hypogonadism. If the hypofunctioning is mild, retarded growth of the long bones is associated with cross-striations in the metaphyseal regions similar to those found with serious illness or hypothyroidism.

Hypogonadism. Postmenopausal Osteoporosis

Painful osteoporosis may ocur in women at the menopause, which is either in the natural form or following castration. When the menopause is physiologic, the interval is usually several or more years following the cessation of the menses (on the average of about nine years) When artificial menopause is produced, the symptoms may occur within a year The spine and pelvis are usually affected. There is progressive rarefaction, which may lead to crushing and fracture of the vertebrae Herniation of the nucleus pulposis has been reported. The increased urinary calcium excretion may lead to urinary calculi. The disease has an insidious onset, with pain and neuralgic symptoms. The diagnosis is confirmed by the response to estrogens. Reossification occurs under this treatment.

Hyperthyroidism

In this condition, calcium excretion is increased, but the serum calcium and phosphorus are normal. Demineralization of the bone may appear in the spine and flat bones and ultimately there is loss of density in the long bones. Kyphosis may result and, rarely pathologic fractures. The disease is usually of four or five years duration before bony changes are evident. Pain is an outstanding symptom. An appearance in the femur similar to that found in Gaucher's disease, has been described. The bony abnormalities disappear when the thyroid disturbance is corrected.

Hypothyroidism

In congenital hypothyroidism, or cretinism, the child has a swollen face, a thick tongue and a protruding abdomen. There is deficient mentality weak musculature and dwarfism The growth of bone is arrested and the union of the epiphysis is delayed. There is delay in the closure of the fontanelles and the dentition is defective. The delay in the bone age of the cretin distinguishes this developmental deficiency from mongolism. Less severe hypothyroidism in childhood is accompanied by myxedema and retarded bone growth of a milder character This condition must be differentiated from sexual precocity in girls, in which there is a low metabolic rate but no retardation of bone growth. The diabetic child with insufficient insulin may have retarded bone growth, simulating hypothyroidism. In hypothyroidism and cretinism, there may be disturbance of the epiphysis of the femur with typical Legge-Perthe's disease.

In adult hypothyroidism, there may rarely be increased density of bone, due to retention of calcium.

Varieties of Osteoporosis

Osteoporosis may be defined as that disturbance of bone in which there is decreased production of osteoid tissue by the osteoblasts. Osteoblastic activity can be influenced by steroid hormones, mechanical stresses and strains and certain nitrogenous substances.

In osteoporosis of old age of either sex,

in the postmenopausal state and in Cushing's syndrome the steroid hormones are affected. The steroid hormones involved in stimulating osteoblasts are (Albright) (a) adrenal cortical "N" hormone (b) estrogen and (c) testosterone. There is one steroid hormone which inhibits the osteoblasts, the adrenal cortical "S" hormone

The explanation for the stress and strain factor is predicated upon the thesis that the skeleton adds to itself in order to withstand stresses and that osteoblastic activity is spontaneously activated when the skeletal structure is unstable

Osteoporosis is a common finding in starvation and malnutrition. Serum albumen is cited as a possible important nitrogenous precursor which is depleted and adversely affects the production of the bone matrix.

Osteoporosis of Disuse Disuse is a part of the stress and strain factor in osteoporosis. Albright suggests that the skeleton adds to itself in order to withstand stresses. This stimulus is removed in the fixation or nonuse of the part, for whatever reason, and gives rise to osteoblasts which stop producing. Overfixation of the part and many diseases, such as various forms of arthritis, ochronosis with osteoporosis, Marie-Strumpell, Bechterew's disease and paraplegia may produce disuse atrophy The factors associated with senile osteoporosis may also play a role.

Senile Osteoporosis is characterized by weakness, easy fatigue nervousness, dull ache in the spine with, frequently sudden onset of pain usually in the lower part of the throacic region or in the lumbar region in elderly people. The roentgen studies reveal that the majority of changes are in the vertebrae. There is frequent marked decalcification with compression of vertebral bodies in their anterior portions. Nonuse plays a role in the development of senile osteoporosis, which may be partly attributable, also to the loss of gonadal hormones and to the cortico-adrenal osteoblastic stimulating hormone (Albright) Space does not permit the listing of many of the commonly proposed etiologic factors in senile osteoporosis which seem to us somewhat inadequate.

Postmenopausal osteoporosis occurs in women after the menopause, though occasionally similar lesions are noted in the male The average time of onset in Albright's series was nine and a half years, after an uncomplicated physiologic menopause. As described above, the osteoporosis has a predilection for involving the spine and the pelvis the long bones and skull rarely are affected. The beneficial effects obtained through the retention of calcium by estrogen therapy is an important argument for its etiologic role

Malnutrition osteoporosis is a common finding in states of starvation and malnutrition. There is considerable evidence to indicate that certain nitrogenous elements are necessary in the production of bone matrix. Serum albumen is felt to be an important nitrogenous precursor and a deficiency of this precursor is found in starvation and in malnutrition when osteoporosis is present. This, of course, is in addition to the presence of osteoblasts, subject to stimulation by the anabolic steroids and also stresses and strains.

Posttraumatic painful osteoporosis is characterized by partial loss of function of the affected part, varying degrees of vasomotor and trophic changes and spotty demineralization of the skeleton in the region of the trauma. Disturbances of function and aching pain are out of proportion to the trauma inflicted. The disease may be divided into three groups

Painful osteoporosis with slight trauma to periarticular regions, coming on gradually over a four week period.

2. Painful osteoporosis which follows injury to the articular or periarticular tissues, usually with a fracture of one or more bones in the extremity

3. Painful osteoporosis which follows moderate trauma to soft parts about the joints

The mottling of the bone is usually more marked in the carpal and tarsal bones and the heads of the metacarpal and metatarsal bones (see Kienböck's and Köhler's disease, Chap. 27) The cortex is thinned and the lamellae become indistinct. The absorption of bone seems to spread the limits of bones seem to be lost, ultimately repair sets in and symptoms clear up Roentgenograms made much later however show some evidence of osteoporosis. Periarterial sympathectomy in the hands of Herrman has done most to relieve symptoms and shorten the course of the disease, especially when performed in the acute phase of the malady

Kummell's disease is an osteoporosis associated with a symptom complex which follows trauma either directly or indirectly to the buttocks, head or shoulders while the spine is erect. A linear fracture of the vertebra occurs and frequently is over looked or cannot be seen in the roentgenogram. Osteoporosis appears in the involved vertebra, which may ultimately lead to spontaneous vertebral collapse with localized pain, kyphosis or gibbous formation, with or without cord disturbance.

Melorheostosis (Léri)

An anomaly of ossification appearing in the bones of a single limb has been described by a group of authors beginning with Léri,* Putti, Lewin and others. The disease is a flowing hyperostosis in which irregular wavy new bone simulating the molten wax of a candle descends along one margin of a long pipe bone, extending downward from the hip or shoulder (Fig 634) The first symptoms appear in childhood or in young adults, the oldest age of onset reported being 42. The symptoms are rheumatic pain, limitation of motion progressing to the point of complete fixation of the joint and occasionally edema due to pressure upon the blood vessels. The disease is extremely chronic, but tends to become arrested and shows no relation to malignancy

The roentgenogram must be differentiated from traumatic or infectious ossifying periostitis, myostitis ossificans and osteogenic sarcoma. The diagnosis of melorheostosis depends upon the dense irregular and prolonged tract of ossification proceeding from the hip or shoulder joint downward in a linear tract along a single margin of more than one bone of an extremity The dense calcification in the region of a joint with spotty shadows in the soft part is typical.



Fig. 634. (No. 33958) A case of melorheostosis showing dense, irregular new bone formation and a characteristic limitation to one side of the bone. This process has remained stationary for seven years.

Operative treatment is not called for The pain yields to rest upon immobilization, and limitation of joint motion can rarely be avoided. Otherwise the prognosis is unqualifiedly good. Histologic studies have shown only peculiar elongated spicules of

* Léri, A., and Lièvre, J. A. La mélorhéostose, Presse méd. 36 801 1928.

new bone formation and an absence of in flammatory tissue. There is no known eti ology Only sixteen cases had been reported in the literature up to 1932 (Kraft)

OSTEITIS DEFORMANS

Paget s disease of the skeleton affects pri *marily male* adults, usually past the age of



FIG. 635. (No. 40728) A case of *Paget s osteitis deformans involving the skull, pelvis, femora and tibiae Note* the widening and roughening of the tables of the skull, spoken of as of "nig ger wool" appearance.

45 The bone involvement is most often multiple, affecting the tibiae, skull and pelvis, in the order of frequency given. The femurs are also prone to involvement. When the disease occurs as a single lesion, the tibia is usually affected. When it is gen eralized, the spine and sacrum are sooner or later involved. The clinical appearance of the patient in an advanced case is char acteristic. The skull is enlarged and square across the front, and deafness may result from the osseous changes. The tibiae are bowed forward, and the femurs bent later ally the pelvis is widened and a gradual lordosis affects the spine varicose veins are present in the lower extremities, and tor tuous sclerotic arteries are common.

Kraft, E.: Melorheostosis Léri, J.A.M.A., 98 705, 1932.

In the roentgenogram the characteristic appearance of the skull is described as "nigger wool" The bones of the calvarium are thickened from two to five times and are



FIG. 636 (No. 40728) Shows a characteristic anterior bowing of the tibia in Paget s disease

made up of areas of varying density with a very fuzzy inner and outer table. The tibiae are bowed, and the cortex added to by new bone formation of decreased den sity in the subperiosteal zone. Cyst forma tion may occur beneath the cortex and most commonly is located in these bones of the leg (Fig 635 and 636) *The pelvis and fe*murs, when involved, present similar fea tures. The bones are widened by new bone of decreased density Cysts are more fre quent in the tibiae.

Histologically the basis of the disease is bone absorption replaced by ossification of a low order Under the microscope giant cell osteoclasts may be seen destroying old spicules of laminated bone, while at the same time there is an increase of young, loose connective tissue, permeated by many young capillaries, with the formation of new coarse membranous bone (Fig. 637) This new coarse bone replacing the old denser bone leads to an enlargement and elongation of the bones, accompanied by bending Pathologic fracture occurs, but is not frequent and has been recorded in only isolated cases.

One of the important complications of Paget s osteitis deformans is malignant disease. Sir James Paget,* who originally described this disease in 1876, was struck by the frequency with which malignancy occurred in the cases which he reported. Carcinoma associated with this disease is probably accidental, and, without doubt, in some cases recorded the entire skeletal changes have been due not to Paget s disease but to metastatic carcinoma. The resemblance of metastatic carcinoma to Paget s disease may be quite marked.

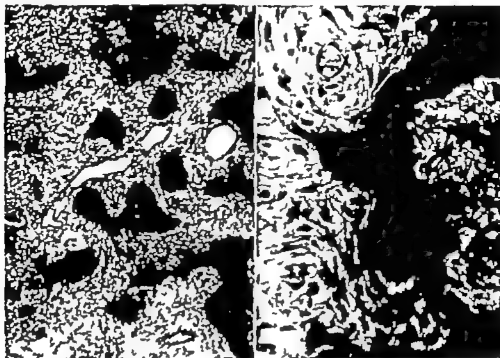


FIG. 637 (No. 36068) Photomicrographs showing the pathologic changes in Paget s osteitis. The spicules of new bone can be seen undergoing secondary resorption through the activity of giant-cell osteoclasts. Both low and high magnifications are shown.

In the roentgenogram the differential diagnosis can usually be made because metastatic carcinoma, despite the new bone formation about the cortical zone, always produces lytic changes in the medullary cavity whereas this is not the rule in Paget s disease. The smooth, expanded cortex of osteitis deformans in the long bones is distinctly different from the irregular margins of this zone seen with carcinomatous metastases. Involvement and bowing of the tibiae are common in Paget s disease, but rare in metastatic carcinoma, while lung metastases are absent in Paget s disease but occur in carcinoma.

Differentiation between these two conditions is extremely important from a prog

* Paget, Sir James On a form of chronic inflammation of bones (osteitis deformans) Medico-Chirurgical Trans. 60: 37 1877

nostic standpoint, since a pessimistic or fatal prognosis based on the assumption of skeletal metastases may prove exceedingly embarrassing to the physician if the patient has a true Paget's osteitis and outlives all expectations. Blood phosphatase determinations are important in diagnosis. In Paget's disease, blood phosphatase is usually 30 or more units per 100 cc. (normal 1–3 units, Bodansky scale) The phosphatase is higher in this disease, in our experience, than in any malignant change affecting bone.

In from 5 to 7 per cent of the cases of Paget's disease malignancy in the form of sarcomatous change takes place in the bones affected. This form of sarcoma is generally periosteal in type, and may be of the chondral, osteolytic or osteoblastic variety of osteogenic sarcoma. Unless such a complication supervenes, the prognosis for life is good, and the degree of discomfort is rarely severe.

Osteitis deformans may be preceded by localized rarefaction in the skull and long bones. This incipient phase of the disease is known as osteomalacia circumscripta. White and Stein (personal communication) believe that in the early phase of Paget's disease, which resembles osteomalacia or rickets, the condition can be benefited by administering Vitamin D The characteristic bone changes seen in advanced cases, however result from successive waves of reossification superimposed upon preceding faulty ossification. In this stage of the disease a decalcifying diet (prohibiting milk, cheese and eggs) and the administration of magnesium carbonate by mouth are helpful, if not continued beyond six months.

In some cases of Paget's osteitis the initial changes are in the bones of the face. These changes referred to as leontiasis ossium may begin in adolescence and progress over many years. Later the long bones, spine and sacrum show the characteristic features described above. Such cases have been reported in a previous chapter dealing with lesions of the jaws (Chap 23) Hamburger and Nachlas reported such a case in 1926.* These cases are difficult to distinguish from isolated instances of osteopetrosis (marble bones) occurring in adults (Schwartz) †

Osteomalacia

A disturbance in the lime salt content of the bones leading to softening and consequent bending and deformity in an adult is referred to as osteomalacia. If the condition is associated with pregnancy in women between 20 and 40 the diagnosis is usually accepted as confirmed, but if male adults or women past the menopause are affected and multiple cysts are also present in the bones, the case is more apt to be classed as von Recklinghausen's generalized osteitis fibrosa. In the past the clinical concepts of von Recklinghausen's disease and osteomalacia have been ill-defined. However since 1900 the works of Askanazy Erdheim and many recent contributors have restricted von Recklinghausen's disease to cases of disturbed calcium and phosphorus metabolism in which parathyroid tumors accompany cystic changes in the bone These osseous changes may be definitely relieved by parathyroidectomy On the other hand, osteomalacia, although presenting similar osseous changes, is associated with an external factor dietetic deficiency and may be relieved by the form of therapy successfully applied to rickets. In osteomalacia as in rickets the blood calcium is decreased, whereas in von Recklinghausen's disease there is a hypercalcemia. Blood serum calcium values between 16 and 23 have been reported in von Recklinghausen's disease with parathyroid disturbance, while in osteomalacia the value may fall as low as 5 mg per 100 cc.

Multiple cysts of the bones are not frequently associated with osteomalacia. Al

* Hamburger L. P and Nachlas, I. W : Leontiasis ossea as a manifestation of Paget's Disease. Arch. Surg. 12 727 1926.

† Schwartz, C. W : Cranial osteomas from a roentgenologic viewpoint, Am J Roentgenol. 44 188 1940.

though this condition is most easily recognizable in women in the child-bearing age, the senile form occurs in both males and females after the age of 60. Improvement is apt to follow the menopause in women



FIG. 638. (No. 46588) Roentgenogram showing bending and distortion of bones in osteomalacia.

affected during pregnancy. In progressive stages of the disease however pain increases with the deformities, and disability is often marked enough to keep the patient bedridden. Where males or women not of the child-bearing age are affected, a search should be made to rule out parathyroid tumor and careful blood-chemistry studies should be made.

In the roentgenogram the most characteristic appearances are the deformities which affect the thorax, pelvis and the long bones. Compression of the pelvis is due to the weight transmitted through the femurs upward and from the spine downward. In accordance with this, the sides of the pelvis are pushed inward and the sacrum forward and downward.

In the long bones the deformities generally follow fracture and healing. The layers of compact bone are gradually absorbed until the cortex is paperlike in thinness and the entire bone is coarse, cancellous and

nearly transparent. Cysts may occur in the marrow cavity thus increasing the deformity and the liability to fracture (Fig 638) At times, *spontaneous regression* and healing take place, and we have seen such large evacuated areas in the skull disappear without treatment. The treatment is dietetic with increase in the calcium and phosphorus intake and the administration of ergosterol.

In recent years, osteomalacia has been specifically defined as a deficiency disease affecting bone, in which both lack of vitamin D in the food and deficient intake of calcium and other minerals are present. If vitamin D only is deficient, the condition is spoken of as late rickets. If there is mineral deficiency without vitamin D deficiency the condition is referred to as "hunger osteoporosis." From a practical standpoint, however the combination of vitamin D and mineral deficiency is most common and osteomalacia is therefore the most important clinical entity in the group.

In osteomalacia, the Ca and P content of the bones is markedly diminished, but the relation of Ca to P remains about normal. The magnesium content of the osteomalacic bone, however is increased. In the four cases of hunger osteopathy examined by Loll, the P content was much more depleted than the Ca, and the amount of magnesium remained about normal.



Fig. 639 (No 60554) Roentgenogram showing linear form of osteopoikilosis.

Osteopoikilosis

In this disease, small foci of condensed bone are scattered within the cancellous spaces. The long bones of the skeleton are usually *affected*, particularly in the region of the hips and shoulders. The small compact masses are numerous and are aggregated near the ends of the bone. The age of onset is unknown, as the disease is symptomless and is usually discovered on routine roentgen examination. The dense areas do not enlarge with age *but become progressively* more opaque on roentgen examination. *Microscopically* they consist of normal bony trabeculae of increased thickness and with diminished intervening marrow *There is no disturbance of the blood* calcium or phosphorus levels. There is usually no *association* with scleroderma, such as has been suggested by some reports in the literature. No treatment is required. Roentgenologists have classified the condition into two types: the punctate or nodular form, in which the spots are accumulated at the end of the bone, and the linear in which the shadows are arranged longitudinally (Fig 639)

Milkman's Disease

Milkman, in 1930 reported a case of multiple spontaneous symmetrical fractures





FIG. 640. Roentgenograms showing the nodular form of osteopoikilosis in the shoulder and pelvic girdles.

which involved the flat and tubular bones. Additional cases have rapidly accumulated. The symptoms of the condition are those of progressive difficulty in walking and pain in the lower back and extremities. Skeletal lesions consists of transverse zones of radiotransparency which are decalcified, leading to fracture and displacement of fragments. There is no evidence of repair or callus formation. No changes are found in the blood serum levels of calcium or phosphorus and there is no known etiologic factor Milkman's patient had 43 fractures. The most severe deformities occur when the region of the femoral neck is affected. The least disabling lesions are multiple transverse fractures of the rib The disease is progressive, with periods of intermissions and exacerbations. The prognosis is poor Hopf has reported striking results with large amounts of vitamin D and calcium therapy

TOXIC DISEASES OF BONE

Radium Poisoning

Radium poisoning is a rather inaccurate term referring to injury to the bone and the hematopoietic tissues following the ingestion of radioactive substances. In dial painters, before the days when proper precautions were instituted, thorium dioxide with some mesothorium was the ingested material and the damaging agent was the alpha irradiation In early days, radium



FIG. 641. Roentgenogram showing multiple transverse fractures of the ribs and fibulae in a case of Milkman's disease.

salts were administered and Stevens reports a patient living 18 years after the administration of 440 micrograms of radium. With the introduction of the atomic bomb so-called radium poisoning may result from any of the long-lived artificial radioactive isotopes. With the exception of beryllium these are all beta or gamma emitters.

In the poisoning that occurs in dial painters, roentgenograms show hypercalcification at the metaphysis, similar to poisoning with lead or bismuth. However the continuous alpha irradiation stimulates an actual osteitis, which may go on to osteogenic sarcoma, if the patient does not die of thrombocytopenia, leukemia or anemia first. This period may be fifteen or more years. The diseased bone is gradually replaced by new bone. If an infection is superimposed upon the process, a severe osteomyelitis results. This is particularly apt to happen in the region of the jaws because of the teeth.

One microgram of radium retained is enough for destructive action. Steven's patient is well 18 years after retaining 11.4 micrograms out of 440 micrograms (2.5 per cent). She recovered from an osteitis of the jaw.



Fig. 642. Roentgenogram of chronic lead poisoning in a child. Note the transverse zones of increased density behind the epiphyseal lines.

Lead and Bismuth Poisoning

Visible changes following lead poisoning occur in children and infants. The changes involve the metaphysis of the long bones and the margins of the small bones, appearing as bands of sclerosis. The band is caused by a deposition of lead salts. These tissues assay four times the content of remaining bones for lead. Bismuth produces similar effects.

Phosphorus Poisoning

Phosphorus poisoning is due to the absorption of yellow phosphorus in small doses over a long period of time and leads to osteosclerosis at the metaphyseal ends of growing bones and rings small flat bones. Acute phosphorus poisoning produces osteitis of the mandible.

Fluorine Poisoning

The allowable fluoride content of water is 1 to 1,000,000. Excess amounts of fluoride in the water or exposure to fluorides in smelting or quarrying leads to deposition of calcium fluoride or magnesium fluorides in bones, which stimulates osteosclerosis.

Caisson Disease

Caisson disease is characterized by multiple areas of necrosis in the bones and the joint surfaces, the result of air emboli. These are followed by healing with bone sclerosis. Similar lesions may occur on rapid decompression in divers and high altitudes in fliers.

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29

Therapeutic Measures in Malignant Lesions of Bone

In Parts I and II prognosis and treatment have been considered in relation to the form of bone tumor discussed in the individual chapter

The present chapter discusses the indications for and the relative values of the therapeutic measures available in the treatment of malignant diseases of bone.

During the diagnostic survey of a patient in whom a malignant bone lesion is suspected it is a good plan to keep the part at rest. Harm may be done by not taking this precaution. When the lower extremity is involved, the patient may walk on crutches The involved upper extremity may be put at rest in a sling When the lesion is in the skeletal trunk, it is wiser for the patient to rest in bed, especially is this true when the trouble is in a vertebra. In such cases a cast or traction should be applied.

In a study of cured cases of bone sarcoma, regardless of the type of sarcoma or the form of treatment, there are practically no cures reported of sarcoma of the skull (lower jaw excepted) the vertebrae or the pelvis. In all the other bones, five-year survivals have been recorded in from 10 to 35 per cent.

Regardless of the type of sarcoma, local excision or curettement alone has not accomplished a cure, and irradiation alone has rarely sufficed. The choice of treatment, therefore, unless palliative, must lie between resection or amputation alone, or surgery combined with forms of irradiation.

The great majority of permanent cures have resulted from resection or amputation, with or without pre- or post-operative irradiation. Resection proves at times effective in the mandible, ribs, clavicle, in the bones of the upper extremities, in the fibula and occasionally in the tibia, and its effectiveness may be enhanced by preoperative irradiation, particularly in Ewing's sarcoma. Amputation leads as a method of treatment in the permanent cures of patients with tumor occupying any part of the tibia or lower end of the femur Its effectiveness is not enhanced by pre- or postoperative irradiation. In sarcoma of the upper humerus, resection with an attempt to save the function of the arm is the treatment of choice, since those tumors which cannot be removed by resection are usually not cured by any form of operation. Sarcoma of the upper femur is usually incurable by amputation and disarticulation must be practiced for a permanent cure. Irradiation in this location is palliative. Biopsy preceding resection or amputation by an interval of several days, is not detrimental to cure. But incomplete removal, unless immediately followed by adequate irradiation, destroys the effectiveness of more radical surgery when this is instituted at a later period.

The histologic composition of the tumor is an important determining factor in the outcome of the disease. Each of the different histologic types has a different prognosis and presents individual problems in treatment.

In the undifferentiated forms of osteolytic and chondromyxosarcoma taken as a group, permanent cures comprise approximately

10 per cent, and early amputation or radical resection is the treatment of choice. The higher degree of malignancy and low percentage of permanent cures favor such radical procedures. Where amputation is not possible because of the location of the growth or because of inability to secure the consent of the parties involved, irradiation should be given. Recent experience shows that some patients, particularly those with osteolytic sarcoma remain well for a period of over three years under irradiation even when a primary curettement or excision has been done through error in diagnosis or through necessity In such cases of irradiated osteolytic sarcoma estrogen and calicum therapy add to the effectiveness of palliation and life may be prolonged.

In chondrosarcoma or osteolytic sarcoma secondary to a preceding benign lesion of bone, the patient may live beyond the five-year period, following local excision with the cautery and postoperative irradiation. In both types of sarcoma, however the patient eventually succumbs to metastasis. There have been a few exceptions in secondary chondrosarcoma, but the difficulty in differentiating between recurrent chondroma and secondary chondrosarcoma pathologically may account for these cases.

Tissue differentiation, resulting in growth restraint, is a most important factor in altering the prognosis, despite the tumor's possible inherent radioresistance or sensitivity It is this underlying factor which permits repeated insults to certain tumors, and in spite of them, the patient survives in a number of instances.

Ferguson decries early amputation and points out the number of patients with "osteogenic sarcoma" who survived although frequently they had late amputation, often with preliminary roentgen treatment, repeated excisions or partial resections before amputation was performed. He suggests the possibility that these procedures may have had a favorable influence upon the course of the tumor We cannot accept this point of view

If one separates osteogenic sarcoma into the various entities detailed elsewhere in this book and considers the prognosis and treatment of each, and if one further considers the tissue differentiation of each, with its relative aggressiveness, it would seem that the following points are fundamental

1 Regardless of the type of sarcoma (Ewing's tumor and paravertebral neuroblastoma excepted) irradiation alone has rarely sufficed to accomplish a cure while combined with resection it has offered better results.

2. Amputation is favored as a method of treatment.

3. Tumors with long preoperative symptoms are less aggressive in character and the patients survive in larger numbers.

4. Tumors with short preoperative symptoms usually connote a more aggressive process, with a reduction in the number of survivals.

5 The primary bone sarcomas which show the greatest tissue differentiation yield the largest percentage of cures when treated adequately

6. Early diagnosis and radical treatment are to be recommended.

RADIOSENSITIVE FORMS OF SARCOMA

Experience has been our best teacher as to the behavior of tumors under radiation. A bitter lesson has been learned in that radiosensitivity does not parallel radiocurability The term "radiosensitivity" is a relative one The radiosensitivity of a tumor depends upon both the histologic characteristics of the tumor cells and the nature of the surrounding tumor bed. It cannot be determined by microscopic examination alone There are innumerable factors to be considered, some of which are not clearly understood at the present time.

Practical knowledge of radiosensitivity has been gained by trial and error correlating the effect of treament upon the tu

mor cells, the variations in the surrounding medium of the tumor and the ultimate results.

Radiosensitivity increases with the embryonal quality of the tumor or anaplastic changes in the tumor This statement must be qualified immediately for those tumors which seem to have inherent radioresistant growth properties.

The tumor bed is of great importance, and where cartilage and bone are concerned, two factors make for radioresistance (1) very little reaction to irradiation by the individual cells (2) an avascular type of tumor bed. Edema and infection also increase resistance.

In the 8 cured cases among 27 of **chondroblastomas**, amputation was performed once for a tumor in the lower radius, resection, once, for a tumor in the upper humerus curettement for another in the upper humerus, and deep roentgenotherapy in the remainder The amputation and curettement were supplemented by pre- and post-operative irradiation. In the case curetted, a radium capsule was inserted directly into the wound. The cured cases are too few in this group to enable us to draw conclusions, but the data together with more recent observations, suggest that the tumor presents a degree of radiosensitivity

Ewing s sarcoma is extremely sensitive to irradiation, yet the curability of the disease is far less striking In our experience it is best treated by radical surgery which offers about 20 per cent of five year survivals. Unless the irradiation has been combined with radical removal, it has sufficed to establish less than 10 per cent of permanent cures. Primary amputation in the earliest stages has offered the most for cure

Meyerding, however in a recent report indicates that of 57 patients treated by irradiation alone, 11 patients (23.4 per cent) have survived five years. With the increasing accuracy of the application of roentgen-ray beams, it is becoming apparent that this disease may be favorably influenced by roentgenotherapy One should not be misled, however by a favorable response to less than full therapeutic amounts of roentgenotherapy It is our experience that in a certain number of cases if roentgenotherapy is relied upon without adequate operation at the optimum time it will produce an inoperable and hopeless lesion.

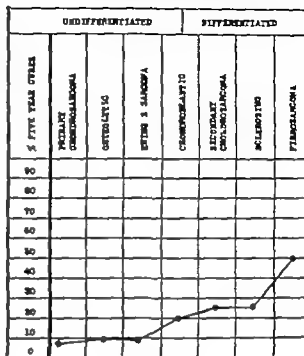


CHART 18.

In lymphomas of bone irradiation with roentgen rays is an effective form of palliative roentgenotherapy The patients do not tolerate well heavy doses of irradiation to all the involved nodes. Suberythema or fractional doses of roentgenotherapy should be given to the affected nodes. The large lesions of bone may be greatly improved by a single large suberythema dose or by repeated fractional doses of high-voltage roentgen rays. In the terminal phases of the disease, however routine irradiation is not advised.

Radioactive phosphorus has been used with good effect in certain blood dyscrasias. It has been of greatest value in controlling

the clinical and hematologic manifestations of polycythemia rubra vera. It has also been found to be a valuable adjunct in some of the more chronic leukemic states, especially in those cases which have become intractable to roentgen irradiation. Hodgkin's disease and lymphosarcoma have not been effectively controlled by this therapy Radioactive manganese has been more effective in controlling Hodgkin's disease (Motley) *

Goodman and others have used some of the nitrogen mustards in both Hodgkin's disease and in lymphosarcoma. The compounds used were the water-soluble salts of the tris (B-chloroethyl) amine and methyl-bis (B-chloroethyl) amine. These compounds were used in radiation-resistant and advanced stages of the disease. Frequently some benefit was obtained and occasionally clinical results were somewhat dramatic. The general experience, however with these substances indicates that they are too toxic and too ineffective for use in the earlier stages of the disease. To a small extent nitrogen mustards have proven useful in polycythemia rubra vera and in chronic lymphatic leukemia. Both radioisotopes and nitrogen mustards must be considered as adjuncts to roentgen therapy

Urethane depresses the leucocyte count in some cases of leukemia. So far there is no indication that permanent benefit may result from use of this drug in either myeloid or lymphatic leukemia. It can, however be said that the palliative effect is excellent in many cases. The drug is toxic and side effects must be carefully watched for The dosage is 1 to 3 grams daily for several weeks, depending on the response observed. The blood count should be taken every other day

In metastatic carcinoma of the bone, roentgenotherapy remains the bulwark of defense. The palliative results achieved are often striking Pain is relieved and not infrequently weight-bearing bones are sufficiently healed to permit the patients to become ambulatory To obtain optimal results, treatment should be given before the vertebrae are crushed or pathologic fractures of the long or flat bones occur It is our practice to use divided doses of roentgenotherapy daily giving a total of from 1,200 to 1,500 roentgens to a single area. If the vertebrae are crushed or pathologic fracture has occurred, orthopedic measures should be taken similar to those used for traumatic fractures. Following such treatment, irradiation is carried out. When osseous metastases have been treated, it is important that normal activity should not be resumed until roentgenograms reveal adequate healing of bone. After the spine has been treated, adequate support should be continued for from three to six months and thereafter it is a good policy to use some type of ambulatory orthopedic appliance, such as a Bennett brace or corset.

Forms of *metastatic mammary carcinoma* respond to specific forms of therapy other than irradiation. Testosterone propionate is effective in the temporary control of mammary carcinomatous deposits in the bones of female patients. The destructive areas heal with the formation of new bone. The pain and disability are relieved for varying periods of time. We have been using testosterone propionate as pellets, buried subcutaneously in the amounts of 225 mg. at one insertion. The total dose administered in some cases has reached 4000 mg in a period of three months. In a number of the patients hirsutism and deepening of the voice have been encountered. Amenorrhea has been produced in those women in whom menstruation has been present before instituting the therapy An increase in libido has been found in some instances. Alkaline phosphatase has been increased in some of the patients undergoing treatment. The effect of testosterone on the primary breast cancer and soft tissue invasion has been disappointing.

Roentgen castration and surgical castration favorably influence bone metastases in

* Motley L.: Some observations on the use of radioactive isotopes in therapy Memphis M. J 23 155, 1948.

from approximately 13 to 15 per cent of patients who receive such therapy There seems to be no appreciable difference in the percentage of improvement between roentgen castration and surgical castration in our series of cases. However we have not observed a sufficient number of surgical castrations fully to evaluate this mode of castration Castration by either method gives only temporary improvement by re tarding the growth process although strik ing temporary effects have been obtained both in the female and the male suffering from breast cancer The clinical improvement is reflected in the relief of pain, in the radiologic evidence of healing of the bones and, in some instances, in the prolongation of life in spite of the advanced stage of the carcinoma.

Carcinoma of the prostate with bone metastases has been remarkably influenced by castration and by the use of diethyl stilbesterol. The patients become quite comfortable and are able to resume normal activity for varying periods of time Roent genograms show that the bone metastases heal, though subsequent pathologic exam ination usually reveals some residual, viable cancer cells. In some cases, though the pa tient may be freed from metastatic pain in from 24 to 48 hours after orchiectomy evi dence is available to show that the pain frequently returns early and that the relief may be only transitory With the removal of the testes, the androgenic hormone s ef fect on the adult prostatic epithelium is only partly controlled. The next step after orchiectomy is to inactivate the extragon adal androgenic hormones. This neutraliza tion is accomplished by the female hormone diethyl or monomethyl stilbesterol This should be started immediately after castra tion. In determining the correct dosage of stilbesterol, a physician must be guided by the patient s symptoms, the blood acid phosphatase, the physical findings and roentgenograms. It must be pointed out that in both breast and prostatic metastatic cancer to bone, roentgenotherapy is frequently used in combination with hormonal therapy

In **multiple myeloma** roentgenotherapy is an outstanding palliative measure. Con trol of pain and acceleration of healing in pathologic fractures have been accom plished in such treatment. Stilbamidine a hypoglycemia producing drug, has proved useful in the treatment of multiple myel oma. It was first used in the treatment of kala-azar Because both kala-azar and mul tiple myeloma are accompanied by an in crease in the globulin content of the blood serum, Snapper made a trial of the drug in multiple myeloma. As a result of the treatment, multiple myeloma patients were relieved of severe bone pain, and in some of the cases, the progress of the disease was arrested. In two patients pathologic fractures were healed and some of the bone defects were filled out. Clinical improvement has been accompanied in some cases by certain histologic changes in the myeloma cells. Some toxic side effects are noted with stilbamidine but are minimized if freshly prepared solutions are used. Nitrogen mustard and the radioisotopes tried have not yielded encouraging results in the treat ment of multiple myeloma.

High-voltage roentgen rays in multiple malignant lesions of bone are finding a wide application in the larger clinics. Ex ternal radium therapy has been supplanted by roentgenotherapy Interstitial radium therapy has little or no place in the treat ment of bone lesions and frequently gives rise to osteitis and osteomyelitis.

NONRADIOSENSITIVE FORMS OF SARCOMA

Sclerosing osteogenic sarcoma and periosteal fibrosarcoma represent the most highly differentiated forms of bone sarcoma. In all of the cured cases of sclerosing osteogenic sarcoma amputation or radical resection was employed. The tumor definitely is not radiosensitive, and no cure can be attributed to this form of therapy Palliation from pain, however may be derived from ex

ternal irradiation In fatal cases approximately 50 per cent had an incomplete primary operation, followed after an interval of months by ultimate amputation. Two cases cured had amputations following incomplete removal by an interval of months, and in both cases the wound was treated with external radium therapy This emphasizes the point that if incomplete removal is performed through necessity this should be followed by irradiation and ultimately amputation, when possible.

The most highly differentiated and most curable form of bone sarcoma is the periosteal fibrosarcoma. This tumor is not radiosensitive, and is not cured by local excision. In all but one cured case, radical resection or amputation was performed. In one instance excision followed by external radiation was employed. Although no cure results from local excision alone, and recurrence inevitably follows such procedure, an attempt at removal may be made, if the recurrent tumor is promptly followed by amputation.

Neurogenic sarcomas are radioresistant lesions resembling the more benign fibrosarcoma and the undifferentiated oat-cell type of fibrosarcoma. They can only be cured by immediate amputation. In only two instances was cure effected by amputation among this group of tumors.

A study of the cured cases on record in this laboratory show that, in general, biopsy does not influence curability unfavorably The element of risk involved in a properly performed biopsy of bone followed by an interval of 14 days or less before amputation is so small that one is justified in taking this risk and in sending the roentgenograms and sections for consultation, rather than to send the patient on what might prove to be a long and unnecessary journey There is a larger number of local recurrences after biopsy when followed by resection than when biopsy is followed by amputation. If resection is the treatment of choice, an immediate frozen-section report should be available at biopsy so that resection may follow at once

Chondromyxosarcoma and chondroma of the large bones may be unfavorably influenced by biopsy In these tumors there may be fluid or semifluid myxomatous material The escape of such fluid into the wound usually results in rapid local recurrence. Where there is a probability of such a lesion, biopsy should not be performed unless radical surgery is to follow at once. When biopsy discloses a malignant lesion and it is necessary to obtain microscopic confirmation or to secure consent for radical surgery from the responsible party it is best to cauterize the involved area and to follow by deep roentgenotherapy during the interval. It is particularly important to take such precautions when resection rather than amputation is the type of surgery contemplated.

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